European Food Safety Authority

Supporting Publications 2013:EN-428

TECHNICAL REPORT

Outcome of the public consultation on the draft Scientific Opinion of the Scientific Panel on Genetically Modified Organisms providing guidance on the environmental risk assessment of genetically modified animals[1]

European Food Safety Authority [2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

On 18 April 2012, the Panel on Genetically Modified Organisms (GMO Panel) of the European Food Safety Authority (EFSA) endorsed a draft scientific opinion providing guidance on the environmental risk assessment (ERA) of genetically modified (GM) animals. Consequently the draft scientific opinion was released for consultation of the public from 21st of June till 31st of August 2012.

EFSA received 720 comments on the draft scientific opinion from 35 interested parties (i.e. institutes, non-governmental organisations, universities, associations, industry organisations, national risk assessment bodies and individuals). The EFSA GMO Panel, through its dedicated working groups on the ERA of GM fish, GM insects and GM mammals and birds, scrutinised all comments. All the public comments received, falling within the remit of EFSA, were assessed and the draft scientific opinion was revised accounting for the relevant comments.

The scientific opinion in question provides a *de novo* guidance for both applicants and risk assessors on a new and challenging topic. EFSA has committed to publish a technical report on the outcome of the consultation on the scientific opinion. This technical report summarises the most relevant comments received through the public consultation and outlines how these were taken into account in the final document.

KEY WORDS

Animals, birds, Directive 2001/18/EC, fish, genetically modified (GM), insects, mammals, environmental risk assessment (ERA)

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BACKGROUND

The European Food Safety Authority (EFSA) asked the Panel on Genetically Modified Organisms (EFSA GMO Panel) to develop guidance documents for the safety assessment of GM animals that would address both food and feed and environmental safety as well as animal health and welfare issues. Guidance on the risk assessment of food and feed from GM animals and on animal health and welfare aspects was developed by the EFSA GMO Panel, in close collaboration with the EFSA Panel on Animal Health and Welfare (AHAW Panel), and was published on the EFSA website in January 2012 (EFSA, 2012).

To address the request of the European Commission with respect to environmental safety issues, EFSA embarked on various initiatives (i.e. calls for external contractors associated with technical workshops). Three working groups (WGs) were established to develop guidance on the ERA of GM fish, GM insects and GM mammals and birds, respectively. To prepare a *de novo* guidance document, these WGs considered various sources of information, including the reports by external contractors, relevant comments from stakeholders on previous EFSA guidance documents, scientific literature, conference reports, and expert consultation. At its plenary meeting of 18 & 19 April 2012, the EFSA GMO Panel endorsed a draft scientific opinion providing guidance on the ERA of GM animals for further consultation of the public (see Appendix A).

In line with EFSA's policy on openness and transparency and in order for EFSA to receive comments from the scientific community and stakeholders on its work, EFSA engages in public consultation on key issues. The work on the ERA of GM animals is considered to be such an issue. EFSA and its GMO Panel are of the opinion that the ERA of GM animals is a relatively new and challenging topic that needs in-depth discussions on the risk assessment strategies to be applied. Accordingly, the draft scientific opinion was released for public consultation on EFSA's homepage[4] from 21st of June till 31st of August 2012. Stakeholders were informed and invited to submit comments (see Appendix B).

EFSA has committed to publish a technical report on the outcome of the consultation on the draft scientific opinion. This technical report summarises the relevant comments received through the consultation and outlines how these were taken into account in the final scientific opinion.

The EFSA GMO Panel considered all scientifically relevant comments from the public when finalising its scientific opinion. The EFSA GMO Panel did not consider issues related to risk management, risk-benefit, ethical and socio-economic aspects that are outside its remit.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION AND EFSA

Upon request of the European Commission, the EFSA GMO Panel developed a draft scientific opinion providing guidance on the ERA of GM animals. As part of the development process of the *de novo* guidance document, EFSA will consult its stakeholders and publish a technical report on the outcome of the public consultation on the draft scientific opinion.

[4] http://www.efsa.europa.eu/en/consultationsclosed/call/120621.htm

1. INTRODUCTION

At the end of the public consultation period, EFSA had received 720 comments from 35 interested parties (i.e. institutes, non-governmental organisations, universities, associations, industry organisations, national risk assessment bodies and individuals). Comments within the remit of EFSA were considered by the EFSA GMO Panel, in particular by its three dedicated WGs, when preparing the final scientific opinion providing guidance on the ERA of GM animals. The comments related to the draft scientific opinion were compiled with reference to the contributor and the section of the draft scientific opinion to which the comment referred (see Appendix B). Comments submitted formally on behalf of an organisation appear with the name of the organisation.

2. SCREENING AND EVALUATION OF COMMENTS RECEIVED

2.1. General comments

Most of the general comments received were helpful and constructive, aiming at the improvement of the draft text of the scientific opinion. Stakeholders also provided very helpful suggestions for editorial improvements and clarifications.

The draft scientific opinion was deemed quite comprehensive by certain stakeholders whereas others challenged the structure and the length of the document. In general, stakeholders welcomed the numerous details and examples provided in the document but, in some cases, also missed the real message and hence asked for clear and precise guidelines to applicants and risk assessors. Stakeholders pointed out reiterations (i.e. repetitive six steps for each area of risk), inconsistencies and differences in terminology across the different sections of the document. Therefore they called for further harmonisation throughout the whole document in accordance with the objectives and wording of Directive 2001/18/EC (EC, 2001).

Stakeholders wondered why the scope, as defined in chapter 1 of the document, was restricted to some groups of animals (i.e. fish, insects, mammals and birds) and why specific applications or uses (e.g. GM animals for experimental purposes/for pharmaceutical production, GM animals for contained use) were explicitly excluded. In general, stakeholders were of the opinion that the document should not only cover the placing on the market of GM animals but also consider the possible accidental escape of GM animals into the wild. Clarifications were also required on the type of assessment (e.g. data requirements) to be carried out in the case of accidental ingestion or intake of GM insects and their products by humans.

Chapter 5 on Post-Market Environmental Monitoring (PMEM) was recognised by some stakeholders to be too generic; the need for more guidance on the PMEM of GM animals was pointed out.

Certain stakeholders sought more precise guidance (e.g. on sources of information) and consistency for the assessment of the horizontal gene transfer across the four groups of GM animals.

Comments on ethics, socio-economic aspects, possible benefits, and concerns related to traceability, labelling, or co-existence of production systems fall outside the remit of EFSA and therefore were not addressed.

2.2. Specific comments

Major and/or repeated technical comments related to the specifics addressed in the different sections of the scientific opinion (EFSA, 2013) are summarised as follows:

2.2.1. Strategies for the ERA of GM animals

Some stakeholders sought clarifications on the logic and the purpose of the ‘step-by-step approach’, in particular of step 1 (i.e. problem formulation) as described in chapter 2 of the document. They also

made proposals to simplify the text and to avoid repetitions across the sections of chapter 4, describing the specific areas of risk for the four groups of GM animals.

Regarding section 2.2 related to the unintended effects, the requirement for compositional analysis, as one out of the four pillars for the evaluation of possible unintended effects, was deemed too light and should be reinforced. In general, the comparative approach should be further detailed, for example, by elaborating on the types of data needed to assess the interactions between a GM animal and its receiving environments.

2.2.2. Cross-cutting considerations

A generic comment identified the need to clarify how chapter 3 on cross-cutting considerations should be read in conjunction with the other chapters of the scientific opinion (EFSA, 2013).

Specific comments were also received on the following sections of chapter 3:

(1) For section 3.1 on receiving environments, clarifications (e.g. definitions) were requested on the three components of a receiving environment, as well as on the selection process of relevant sites in the receiving environments. A few comments suggested to make clear that the environment comprises also humans and animals living therein.

(2) Regarding sections 3.2 and 3.5 on the experimental environment and experimental design and statistics respectively, stakeholders called for more guidance and proposed to further support these sections by adding literature references. A suggestion to create a new section dealing with modelling requirements was also put forward.

(3) Several comments questioned the approach, explained in section 3.3, for the selection of comparators when the conventional counterpart is not present in the receiving environments of the GM animal (e.g. the insecticide treatments to be used as non-GM comparator for sterile GM insects managing agricultural pests; the use of wild fish of a species closely related to the GM cold-tolerant fish and exploiting similar ecological niche). Some stakeholders also called for clarifications on the differences between interbreeding a GM fish with wild relatives and a domesticated fish with wild relatives and consequences thereof. Comments also pointed out the lack of a sub-section on the selection of comparators for the risk assessment of GM mammals and birds.

(4) The comments received on section 3.4 on non-GM surrogates mainly focused on the quality and quantity of data that applicants should obtain from conducting experiments with surrogates.

(5) For section 3.7, some stakeholders asked to revise and substantiate the different categories of long-term effects and to provide more guidance to applicants and risk assessors on the data sources to inform on possible long-term effects.

(6) Stakeholders commented on the need to read section 3.8 on the uncertainty analysis in conjunction with chapter 5 on PMEM, as well as to account for the possible reversibility of certain effects.

2.2.3. Section 4.1 on GM fish

An overall request for clarifications on the data requirements and the methodology to be used to characterise the hazards was made by some stakeholders, in order to better guide the applicants throughout the ERA process. Definitions of specific terms were also required.

In section 4.1.1 on persistence and invasiveness, more details about the type, quality and quantity of basic information to be provided by applicants were asked together with the need to specify that the

ERA should also assess the consequences of accidental escapes of GM fish from their enclosed aquaculture facilities. Stakeholders requested clarifications and certain modifications to Figure 6 illustrating the staged approach to be followed by applicants for the identification of hazards associated with the dispersal of GM fish and gene introgression and environmental exposure.

A reduction of the "nice to know" information in section 4.1.4 on fish pathogens, infections and diseases, together with the provision of more references and a better formulation of the key question in step 1 were sought. Some comments pointed out the need to consider the possible consequences of a change in the diet of GM fish, compared to non-GM fish, in section 4.1.6 dealing with the environmental impacts of the specific techniques used for the management of GM fish. Furthermore, a few stakeholders were of the opinion that the consequences of GM fish transmitting human diseases or having an altered allergenicity/toxicity potential should be better assessed in section 4.1.7 on impacts on human health.

2.2.4. Section 4.2 on GM insects

A series of similar comments as outlined in section 3.2.3 questioned some generic aspects of section 4.2; for example: that it was not clear where the assessment of potential impacts of GM insects on animal health and impacts of pathogens, infection and diseases associated to the GM insects are addressed.

In section 4.2.1 on persistence and invasiveness, stakeholders pointed out the need for more and clearer data requirements as well as to expand the assessment of the consequences of the transfer of recombinant DNA from GM insects to wild relatives. Clarifications on some definitions (e.g. target organism (TO), sterile insect technique (SIT)) were requested for section 4.2.4 on TOs. Regarding section 4.2.5 on non-target organisms (NTOs), some stakeholders pointed out the fact that NTOs might include harmful organisms and competitors of the GM insects and that more attention should be paid by applicants on the assessment of the receiving environments (e.g. request to improve the selection criteria for focal species). Certain stakeholders also asked to remove the considerations pertaining to environmental benefits from section 4.2.6 addressing the environmental impacts of the management techniques of GM insects.

Numerous comments were received on the need to consider the possible effects on human health of: (1) the accidental intake of GM insects as well as (2) the allergenicity and toxicity of saliva and other fluids injected into human blood by biting or stinging GM insects.

2.2.5. Section 4.3 on GM mammals and birds

General comments expressed the need to make a better use of the case studies described in the introduction of section 4.3. Some stakeholders were of the opinion that section 4.3 was overly complex and was loosing focus on problem formulation. Another observation made was that an assessment of consequences of a population suppression scenario was missing.

Regarding section 4.3.1 on persistence and invasiveness, more clarity on the data requirements was required at different stages of the ERA and also to assess consequences to the environment, after suppression of the target population. Part of the comments to section 4.3.2 on vertical gene transfer acknowledged the need to consider the loss of genetic variability within an animal species, while others challenged it. Under section 4.3.3 on pathogens, infections and diseases, a request to broaden the scope was formulated. Other comments raised included: the need to clarify which type of experiments should be conducted to assess the transmission of diseases, the need to provide additional references to substantiate the requirements listed. As regards sections 4.3.4 on TOs and 4.3.5 on NTOs, the need to include a population suppression scenario was stressed. Other comments indicated the need to harmonise the definition of TOs and to clarify the scope of this section, whereas for NTOs the need to clarify/simplify parts of the text dealing with the selection of focal species was identified. Under section 4.3.9 on impacts on human health, it was requested to assess also potential indirect

hazards (e.g. animals with whom a GM mammal or bird is in contact that would mediate pathogen spread from the GM mammal or bird to humans).

3. INCORPORATION OF THE COMMENTS

3.1. Incorporation of general comments

The mandate from the European Commission specifically asked the EFSA GMO Panel to consider GM animals expected to be on the EU market in the near future. Consequently, EFSA launched open calls for external contractors in order to (1) identify GM animals likely to be marketed in the coming years, (2) to identify the key aspects of the ERA, (3) to collect background information useful for the ERA of GM animals, and (4) to identify scientists with relevant expertise in the field of (GM) animals. The reports by external contractors served as the basis for the development of the scientific opinion (EFSA, 2013). Three WGs were established to develop guidance on the ERA of GM fish, GM insects and GM mammals and birds, respectively. To prepare a *de novo* guidance document, these WGs also considered further sources of information, including the relevant comments from stakeholders on previous EFSA guidance documents, scientific literature, conference reports, expert consultation and the comments received from the public consultation.

The EFSA GMO Panel and, in particular, its dedicated WGs on GM fish, GM insects and GM mammals and birds, discussed the comments at several meetings. Many of the comments received were of scientific value for improving the scientific quality and clarity of the document (EFSA, 2013). These comments were taken into account and the scientific opinion was revised where appropriate.

First of all, numerous comments focused on the need for clearer guidance to applicants, including clarifications on data requirements and harmonisation of the terminology throughout the overall document. In response to those comments, the wording used in the guidance was checked for sake of clarity and the glossary, providing definitions of the key terms (e.g. target organism, animal by-products, propagated pressure) recurrently used in the document, was supplemented. Whenever possible, the content of the scientific opinion was simplified, avoiding repetitions and streamlining some concepts. The wording was aligned with the one of Directive 2001/18/EC.

In addition, chapter 1, where the scope of the document is defined, was revised, in close collaboration with the European Commission, for clarity and consistency with the EU legal framework. Practically, the text of chapter 1 was revised to clarify the different groups of animals and their applications/uses that are covered by the document. The document provides guidance on the ERA of living GM animals to be placed on the EU market, according to Regulation (EC) No 1829/2003 (EC, 2003) or Directive 2001/18/EC (EC, 2001). Applicants should also consider possible accidental escape into the wild of GM animals kept under confined and semi-confined conditions (e.g. enclosed rearing facilities, greenhouses).

Concerning the outline of the scientific opinion (EFSA, 2013), it follows the structure of Directive 2001/18/EC (EC, 2001) and in particular the six steps of the ERA as described in Annex II of the Directive. For sake of comprehensiveness and consistency, the six steps of the ERA were systematically repeated for each area of risk, for the different groups of animals.

In response to the comments related to the harmonisation of the assessment of the horizontal gene transfer across the sections concerned (i.e. sections 4.1.2, 4.2.2, 4.3.2), the EFSA GMO Panel revised and checked the three sections for consistency.

Most of the editorial suggestions were taken on board for the improvement of the whole document.

The scientific opinion was also checked for correct and relevant cross-references between the different sections in order to give a better overview to the readers, and to avoid repetitions.

3.2. Incorporation of specific comments

3.2.1. Specific comments on strategies for the ERA

The EFSA GMO Panel re-considered the 'step-by-step approach' and referred to the European legislation on GMOs, i.e. Directive 2001/18/EC setting up the steps of the ERA of a GMO. In the scientific opinion at stake, similarly to the approach followed for the ERA of GM plants (see EFSA, 2010) and in accordance with the aforementioned Directive, the EFSA GMO Panel further clarified the objective of each step. The scientific opinion highlights the importance of the first step (i.e. problem formulation) of the ERA where, based on the available information, applicants should identify the key questions that the ERA should answer to. The EFSA GMO Panel also revised the order of the various stages of the problem formulation.

Regarding section 2.2 related to the unintended effects, the EFSA GMO Panel followed a 'weight of evidence' approach, consisting of four pillars (1. Molecular analysis, 2. Compositional analysis, 3. Phenotypic assessment and 4. GM animal-Receiving environments interactions), as for the ERA of GM plants (see also EFSA, 2010). In order to address the comments received on the data requirements on the interactions between the GM animal and its receiving environments, the EFSA GMO Panel made clear that unintended effects may be detected through comparisons of biotic and abiotic interactions of the GM animal and the appropriately selected comparators with components of their receiving environments. In this way, the information and data gathered under the sections of chapter 4, contribute to the fourth pillar of the weight of evidence approach.

3.2.2. Specific comments on cross-cutting considerations

In response to the general request for clarifications on how the different chapters of the document are articulated, the EFSA GMO Panel re-considered section 2.3 of the document and revisited figure 2 that provides a structural overview of the document and the interplay between its different parts. It was made clear that cross-cutting issues should be considered by applicants and risk assessors throughout the whole ERA of GM animals, i.e. they should be considered in relation to each area of risk.

The EFSA GMO Panel also addressed the specific comments received on the following sections of chapter 3:

(1) The text of section 3.1 on receiving environments was revised and key definitions were added to improve the clarity of the concept; for example, the definition of 'accessible ecosystem' was reworked, being one of the three components of a receiving environment. It was also made clear that, according to Directive 2001/18/EC (EC, 2001), the ERA is focused on the identification and characterisation of intended and unintended effects with respect to possible adverse impacts '*on the environment, including human and animal health'*.

(2) In response to stakeholders comments on the lack of guidance in terms of modelling as a useful tool for the ERA of GM animals, a new section 3.6 was developed in order to provide guidance on the modelling process in the ERA. The EFSA GMO Panel agreed that the complexity of the biotic and abiotic interactions, the EU legal requirements in terms of animal welfare and animal experiments and the subsequent multiplicity and diversity of questions posed in an appropriate ERA may result in the need to make predictions based on mathematical modelling techniques. The EFSA GMO Panel therefore considered such techniques particularly useful for temporal and spatial upscaling (EFSA, 2010) and for resolving uncertainties where there are data gaps.

(3) In response to the comments on the choice of appropriate comparators when the conventional counterpart is not available or not able to survive in the receiving environments of GM animals (e.g. cold-tolerant fish), the EFSA GMO Panel described the selection process for alternative non-GM comparators under sections 3.3.1 for GM fish and 3.3.2 for GM insects. On the choice of non-GM comparators for GM mammals and birds, it was considered

sufficient that applicants and risk assessors should follow the guidelines provided in the introduction of section 3.3. Concerning section 3.3.1, the text addressing the different genetic consequences of GM fish interbreeding from those of non-GM/domesticated fish was reviewed and clarified.

(4) Regarding section 3.4 on non-GM surrogates, the EFSA GMO Panel considered surrogates as a useful approach for informing the ERA of a GM animal on possible biotic and abiotic interactions. In its scientific opinion (EFSA, 2013), the EFSA GMO Panel provides a list of 'questions' that should be considered by applicants when using a non-GM surrogate to collect data on potential impacts of a GM animal. Nevertheless, the EFSA GMO Panel indicated that, while non-GM surrogates can provide valuable data for the ERA, the suitability of non-GM surrogates – and of derived data – needs to be considered on a case-by-case basis.

(5) In section 3.7 on long-term effects, the examples of data sources (e.g. models, meta-analysis, experimental data with non-GM surrogates, literature), that could be used in the ERA, were revisited and supplemented in order to provide more guidance to applicants and risk assessors.

(6) Concerning the request to link section 3.8 on the uncertainty analysis to chapter 5 on PMEM, the text addressing the interplay between the conclusions of the ERA and PMEM was improved. The concept of PMEM is built into EU regulations as an approach to deal with the uncertainties that are inherent in all risk assessments. The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plans proposed by applicants. The PMEM plan should address the specific risks and critical uncertainties identified in the ERA and also the general uncertainties inherent in the nature of the ERA (e.g. effects of spatial and temporal scales) (see also EFSA, 2011). Applicants should also consider the possible reversibility of effects.

3.2.3. Specific comments on section 4.1 on GM fish

In order to tackle most of the comments seeking for improvement of the methodology and clarity of data requirements, the draft was revised (i.e. better explanation of the concepts and clarification of the terminology used) and supplemented with additional literature references. The whole section 4.1.1 on persistence and invasiveness was redrafted accounting for a more logic ERA approach. In addition, Figure 6 was revisited following a more probabilistic approach and further detailed in order to illustrate a possible way, through the recommended staged approach, to problem formulation, for the identification of hazards associated with the dispersal of GM fish, gene introgression and environmental exposure. In section 4.1.1, it was also made clear that applicants should address the consequences of the placing on the market and *accidental escape*, establishment, gene transfer and changes in the fitness of the GM fish and any recipient of the recombinant DNA.

The environmental consequences of a dietary change of GM fish should be considered by applicants as any other consequences of possible changes in the management of the production and/or release of GM fish (e.g. pathogen treatments, water quality, waste products). Furthermore, acknowledging that fish can produce proteins and other compounds that can cause irritations or allergenic responses to exposed humans working with and handling fish, the text of section 4.1.7 was re-considered accordingly. Against this background, the EFSA GMO Panel worked out guidelines for a more comprehensive characterisation of the hazards (e.g. clear data requirements) posed by a potentially altered allergenicity or toxicity.

The text of certain sections (e.g. sections 4.1.1, 4.1.7) was improved for a better readability and consistency throughout the whole document.

3.2.4. Specific comments on section 4.2 on GM insects

Section 4.2.3 was newly created and is specifically dedicated to the possible environmental impacts due to pathogens associated to the GM insects, while section 4.2.7 addresses the impacts of the GM insects production and/or release on human and animal health.

In order to tackle most of the comments seeking for improvement of the methodology and clarity of data requirements, the draft was revised (i.e. better explanation of the concepts and clarification of the terminology used) and aligned with corresponding sections of GM fish and GM mammals and birds. The whole section 4.2.1 on persistence and invasiveness was redrafted accounting for a more logic ERA approach. Definitions were included in the glossary, such as target organism (TO), sterile insect technique (SIT).

The numerous comments received on the possible accidental intake of GM insects by humans triggered in depth discussions and reconsideration of the draft text. GM animals can be placed on the EU market for (1) food/feed uses (e.g. GM cattle) or (2) non-food/feed uses (e.g. GM insects). The safety of GM animals to be used as food or feed will be assessed following the EFSA GMO Panel guidance document on the risk assessment of food and feed from GM animals and on animal health and welfare aspects (EFSA, 2012). Against this background, the scientific opinion (EFSA, 2013) considers primarily effects of GM animals on human health through routes of exposure other than ingestion or intake; these include ocular and nasal as well as exposure through dermal contact and inhalation. However, applicants should assess the likelihood of oral exposure of humans to GM animals or their products which are not intended for food or feed uses. If such exposure is likely and ingestion or intake will occur at levels which could potentially place humans at risk, then applicants should apply the assessment procedures described in the EFSA Guidance Document on the risk assessment of food and feed from GM animals and on animal health and welfare aspects (EFSA, 2012).

Furthermore, the text concerning the characterisation of hazards, in section 4.2.7, was revised in order to consider the fact that venom or saliva of certain stinging or biting insects may cause localized or systemic allergic or toxic reactions in humans. Applicants should consider different routes of exposure, in particular in the case of stinging or biting insects, if any new (recombinant) protein is expressed in their venom or saliva.

3.2.5. Specific comments on section 4.3 on GM mammals and birds

Following the suggestions made by the public, the EFSA GMO Panel made extensive use of the case studies (as described in the introduction of section 4.3), for the different areas of risk, aiming at clarifying and illustrating the purpose of the problem formulation. Moreover, an assessment of the consequences of a population suppression scenario was introduced in the appropriate sections, namely 4.3.1, 4.3.4 and 4.3.5.

Regarding section 4.3.1 on persistence and invasiveness, the type of data required was adjusted but flexibility is maintained; the terminology (e.g. wild/feral relatives) was defined in the glossary and consistently used throughout the document. The section dealing with modelling was revised and moved to chapter 3 (see new section 3.6). The scope of section 4.3.3 on pathogens, infections and diseases was broadened; some examples, in steps 1 and 2, were modified making best use of the case studies. Additional references to substantiate the requirements listed in this section were introduced. Section 4.3.4 on TOs was redrafted accounting for the suggestion regarding the population suppression scenario and other requests to expand the scope of this part; the definition of TO was harmonised with the ones of GM fish and GM insects. Section 4.3.5 on NTOs underwent small changes, mainly concerning the selection process of focal NTO species. The wording of section 4.3.6 on interactions of GM mammals and birds with the abiotic environment was checked for sake of improvement and consistency with the rest of the document. Moreover, points a), b) and c) of section 4.3.9 on impacts on human health were supplemented in order to assess also potential indirect hazards

(e.g. animals with whom a GM mammal or bird is in contact that would mediate pathogen spread from the GM mammal or bird to humans).

CONCLUSIONS

All comments received through the public consultation were scrutinised by the GMO Unit and considered by the EFSA GMO Panel, through its dedicated WGs on the ERA of GM fish, GM insects and GM mammals and birds, when revising the draft scientific opinion providing guidance on the ERA of GM animals.

Many comments received were very appropriate and of high value. These were all incorporated and strongly contributed to enhancing the scientific quality and clarity of the guidance document.

The EFSA GMO Panel acknowledges the usefulness and quality of a large number of comments and would like to thank all stakeholders for their interest and input to its current and future work.

REFERENCES

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APPENDICES

A. TEXT OF THE PUBLIC CONSULTATION FROM THE EFSA WEBSITE

Public Consultation on the draft guidance document on the Environmental Risk Assessment of genetically modified animals

Deadline: 31 August 2012

The European Food Safety Authority's Panel on Genetically Modified Organisms (EFSA GMO Panel) has launched an open consultation on a draft guidance document on the Environmental Risk Assessment (ERA) of Genetically Modified Animals (GMA).

The aim of this draft Document is to guide applicants and risk assessors throughout a comprehensive safety assessment of GM animals to be released into the environment. This initiative was undertaken in response to a mandate received from the European Commission.

This draft Document provides guidelines supplementing the recently published guidance document on the risk assessment of food and feed containing, consisting or produced from GMA as well as for the health and welfare assessment of these animals.

In line with EFSA's policy on openness and transparency and in order for EFSA to receive comments from the scientific community and all stakeholders, EFSA has launched a public consultation on the draft guidance document.

Interested parties are invited to submit written comments by 31 August 2012. Please use exclusively the electronic template provided with the documents to submit comments and refer to the line and page numbers. Please note that comments submitted by e-mail or by post cannot be taken into account and that a submission will not be considered if it is:

- submitted after the deadline set out in the call
- presented in any form other than what is provided for in the instructions and template
- not related to the contents of the document
- contains complaints against institutions
- personal accusations, irrelevant or offensive statements or material
- is related to policy which is out of the scope of EFSA's activity.

EFSA will assess all relevant comments from interested parties which are submitted in line with the criteria above. The comments will be further considered by the EFSA GMO Panel and taken into consideration if found to be relevant.
All comments submitted will be published. Comments submitted by individuals in a personal capacity will be presented anonymously. Comments submitted formally on behalf of an organisation will appear with the name of the organisation.

B. TABLE OF PUBLIC COMMENTS

Table of Member States and stakeholders comments received during the public consultation on the draft Scientific Opinion of the Scientific Panel on Genetically Modified Organisms (GMO) providing guidance on the Environmental Risk Assessment of genetically modified animals

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
1	Center for Food Safety	USA	5. Post-Market Environmental Monitoring plan	Post market surveliance will be easier for GM animals used for food and feed than it will for GM insect. Labeling should be employed as BOTH an environmental assessment monitoring tool and as a food safety tool. Labeling should be required for: a. All products intended for human or animal consumption using terms such as “genetically modified” for organisms consumed directly, or “produced from genetically modified [name of organism]. If safety concerns are identified in 3 c, such as problems from consuming the food unprocessed or raw, these should be on the label of the product, too. b. If even one ingredient in a food contains GMOs, it should still be labeled. c. Breeders of animals should be required to include genetic engineering status in the pedigree of the animal, including how the genetic engineering was accomplished. [i.e. genetically engineered with genes from Chinook salmon and eelpout through micro-injection, cloned]. d. Developers of genetically engineered animals shall provide a simple test to be used to detect the presence of their genetic construct as part of the labeling and approval process. e. Traceability is required from the point of the genetic engineering through the food being on the table. f. Traceability should also be required for genetically engineered animal products used for animal feed, etc.
2	Center for Food Safety	USA	4.3.9 Impact on human health	Much human contact will be with dead animals, including those that have died before slaughter. I can find no where in the guidance any discussion of the impacts of culled animals on either human or eco-system health. Animal agriculture results in large numbers of animals dying before they are consumed. These animals are often rendered for their fats, and used for bone meal and other products, including cosmetics. A part of the ERA should include the effects of disposing of the animals in various ways. I would add section entitled: Assessment of proper way to dispose of culled animals, including whether they are safe for rendering as animal feed, blood meal, use in cosmetics. This may fit bit into line 6341, Step. 3: Exposure characterisation.
3	Federal Agency for Nature Conservation	DEU	5.2 General Surveillance (GS)	6511-6513: As a first step it has to be checked whether relevant monitoring programs already exists and whether they are suitable to provide the relevant baseline data. If that is not the case, additional surveillance has to be implemented to provide the data needed for GS. 6521: When defining assessment endpoints for GS also the biology/characteristics of the animal, the new trait, the intended use and possible exposure pathways to the environment have to be considered. 6539-6541: As we mentioned above, in our opinion separate guidance for PMEM for the different animal groups is needed. We agree that additionally guidance might be essential on a case by case basis.
4	Federal Agency for Nature Conservation	DEU	5. Post-Market Environmental Monitoring plan	6389 – 6547: Chapter 5 is a good summary of the “Guidance on Post-Market Environmental Monitoring (PMEM) of genetically modified plants” (EFSA 2011). However, no recommendations are included concerning the specific requirements of a PMEM of GM animals. We would like to point out that detailed consideration should be given to the question whether the CSM / GS approach for GM plants suggested by EFSA is in all aspects suitable for the PMEM of GM animals. Animals differ in many aspects fundamentally from plants, e.g. in their biology, locomotion and social behavior. Furthermore, different animal groups can show among each other basic distinctions with regard to e.g. habitat, lifestyle and biology, which require different monitoring approaches. Therefore we recommend the development of specific guidance on PMEM of GM animals respectively separate guidance for the different animal groups. The range of captivity (captive, semi-captive and non-captive) has to be addressed by adequate monitoring methodology. Particularly in the case of GM-animals directly released into the environment the respective receiving environment as well as accessible and potential long-term effects need specific attention when developing the monitoring strategy.
5	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	6384 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.

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6	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	6380 ff.: Cf. comment on chapter 4.3. about mitigating measures.
7	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	6193 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
8	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	6186 ff.: Cf. comment on chapter 4.3. about mitigating measures.
9	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	6075 ff.: Cf. comment on chapter 4.3. about mitigating measures.
10	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	6036-6038: Delete “if available” here, because experimental data are essential. It is hardly seriously possible to predict the composition of faeces of a GM animal and their effect on soil degradation when used as manure just from the characteristics of the GM animal or the GM trait.
11	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	5997 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
12	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	5985 ff.: Cf. comment on chapter 4.3. about mitigating measures.
13	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	5517-5520: It is relevant to know the composition of microorganism in the manure of GM animals compared to the non-GM comparator, but it is equally important to know its chemical composition. Again, the draft guidance lacks a listing of background information required for ERA of GM animals (cf. comment on 593 ff.). Also, please add a cross-reference for the case that manure goes into the field to the problem formulation step in chapter 4.3.6 which deals with soil matter, organisms, structure and processes. 5531-5533: Suggest deleting “It is important to note that an assessment endpoint is not an indicator of environmental conditions but is the ecological resource that is to be protected (Sanvido et al., 2012)”, since in case of ecological resources which are complex and difficult to measure one still has to find assessment endpoints which are indicators. In our opinion the definition is not scientific consensus. 5542 ff.: We do not back the hazard identification which relies exclusively on the genetically modified trait and on morphological, behavioural, developmental, physiological, biochemical etc. changes deduced from it, because it ignores the potential presence of unintended effects. The draft simply expects many GM animals, that will be proposed to be placed on the market, to have species interaction not different from comparator species (5664-5665) and does not require tests for differences in behaviour, development, physiology and biochemistry for the GM animal and its counterpart, which we disapprove. According to this approach it is sufficient that applicants clearly show, rather than provide experimental evidence, that GM animals have species interactions no different from the comparator species (5668-5669) under scenario 1, meaning that it is not necessary to follow the approach (cf. 5734-5735). The possibility for exemptions from the approach in Figure 7 should be deleted (cf. comments on 5732-5735) and applicants be requested to check experimentally the assumptions being made. Again, the shortcoming of the draft is obvious not to be clear about which background information are required for ERA compared to risk assessment for food and feed (cf. comment on 593 ff.) 5724-5725: The draft expects that the applicant normally selects at least one focal species from each relevant functional group for an in-depth investigation. This is not sufficient. When functional groups consist of species belonging to different taxonomic groups, at least one species per taxonomic group should be selected for in-depth investigation.

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				5732-5735: On a general basis the four step approach for selecting focal NTOs for an in-depth investigation is approved. However, much of its worth and usefulness depends on further elaborations which are largely missing and should be added of course. The possibility for exemptions from applying this approach including in-depth investigation should be deleted (cf. comments on 5542 ff.). Replace “Step A Identification of functional groups” by “Step A Identification of functional groups exposed to or interacting with the GM animal” in Figure 7.
14	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	5480 ff.: Cf. comment on chapter 4.3. about mitigating measures.
15	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	5402 ff.: We do not agree that the problem formulation should focus on the likelihood that the TO will evolve resistant mechanisms. Other at least equally important issues to consider are e.g. (i) whether the TO will turn to different hosts; this might be relevant for the production environment as well as for the wild in case the GM animal escapes; (ii) whether secondary pest organisms will inhabit the GM animal; (iii) what impacts the expressed specific protein or antimicrobial compound (cf. 5383-5384) in GM products have on the food and feed chain or in associated by-products, waste and faeces etc. when they enter the environment. Please modify the draft accordingly.
16	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	5340 ff.: Cf. comment on chapter 4.3. about mitigating measures.
17	Federal Agency for Nature Conservation	DEU	Step 3: Exposure characterisation	5274 ff.: Exposure characterisation should consider criminal activities as well (cf. 4706-4707.
18	Federal Agency for Nature Conservation	DEU	Step 2: Hazard characterisation	5213 ff.: Efforts to provide and list specific data requirements for identified hazards are appreciated. Compared to chapter 4.1, the draft is more precise and clear about the kind of required information in some cases (e.g. 5229-5237, 5246, 5300-5301; also 5452 ff.). 5229-5232: Please check whether the provided reference for the design of transmission experiments considers for various rearing and environmental conditions. This is important because they may cause ecological shifts in the microbiome of animals and not until then allow pathogens to manifest (lines 5080-5082).
19	Federal Agency for Nature Conservation	DEU	4.3.3 Pathogens, infections and diseases	5080-5082: Consider referring to chapter 4.3.7. since specific management techniques might bring about ecological shifts in the microbiome of animals which allow pathogens to manifest and cause disease. 5132: We request replacing “under representative environmental conditions” by “all potential environmental conditions”. Otherwise, applicants should be requested to demonstrate the representativeness of the chosen environmental conditions. Please clarify that environmental conditions coves not only rearing environments, but accessible receiving environments as well in case of escaped animals.
20	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	5028 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
21	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	5024 ff.: Cf. comment on chapter 4.3. about mitigating measures.
22	Federal Agency for Nature Conservation	DEU	Step 3: Exposure characterisation	4991-4992: Applicants should be requested to determine whether GM animals differ from their non-modified comparator concerning the amount of shed epithelial cells in their faeces especially when their growth is increased. 5002-5003: The sentence is redundant and should be replaced with “Potential exposure routes to be considered are for example”. The following bullet points should include an example for possible exposure routes for the horizontal transfer from GM mammals and birds to other vertebrates. 5016: This bullet point is not an example for a potential exposure route and should be exempt from the list.

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23	Center for Food Safety	USA	4.3.9 Impact on human health	While this document is primarily for ERA with GM animals, it should be noted that many of these animals will be intended for human consumption or permitted for animal consumption. The should be testing the safety of the animal for human and animal feed including scientifically valid feeding studies on humans and animals that would eat the food. Adequate margins of safety for developing fetuses, pregnant women, growing children. Assessment determine whether food can be consumed raw, whole, or if it should be processed further to alleviate safety concerns.
24	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	4927: It is stated that only natural transformation is known to facilitate uptake and genomic integration of DNA fragments. This is not entirely correct. DNA fragments can also be transferred by transduction or conjugation. Free DNA fragments on the other hand can only be incorporated via transformation. Thus the statement should be clarified by the addition of “free” to “DNA fragments”. For clarification it should also be explained why the other processes by which exogenous genetic material may be introduced into a bacterial cell are not considered. 4949: In order to identify microbial species that could serve as recipients for HGT, the ability of the microorganisms to develop competence should be considered. This is certainly a relevant factor, but it should be kept in mind that the ability to become competent has only been investigated for a very small portion of the known microorganisms. This uncertainty should be mentioned. 4972: The inclusion of the consideration of any positive selection conferred by the transferred trait is legitimate but does not consider the uncertainty that the transferred gene might be subjected to a different, not easily apparent, selection pressure due to a change of function.
25	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	5.2 General Surveillance (GS)	Lines 6515ff: Compare above comments to Lines 6444 – 6451. Not only aspects of the environment but also (animal and human) health related issues need to be addressed within GS. Lines 6539 – 6547: The consideration of the existing guidance for PMEM of GM plants in certain aspects may not be sufficient to provide the necessary guidance to address issues that are case-specific for certain GM animals and application types (e.g. GM animals released in large numbers for non-farm uses). Use of common formats for reporting also is fine, but will not add clarity to applicants how to set up PMEM. Thus more detailed guidance needs to be developed for PMEM of different types of GM animal applications.
26	Federal Agency for Nature Conservation	DEU	4.3.2 Vertical and horizontal gene transfer	4889: The insertion “if HGT can occur” is superfluous and should be deleted.
27	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	5.1 Case-Specific Monitoring (CSM)	Lines 6444 – 6451: It should be mentioned that for relevant GM animal ap-plications, e.g. GM insect applications directed to reduce the vectoring capacity of the respective species for transmission of pathogens, potential health risks and the efficacy of the application need to be monitored in addition to adverse effects on the environment. Lines 6448 – 6451 are contradictory to Lines 6452ff stating that efficacy of risk management strategies implemented for a specific GM animal applica-tion should be determined by the applicant in the frame of CSM. Thus GM animal applications for which “risks and critical uncertainty have been identified in the ERA“ should be subject to CSM, at least to monitor efficacy of the implemented risk management strategies. Lines 6465 – 6476: It should be evaluated whether the indicated statistical approach as regards assumption of a 5% type I error is adequate for all CSM studies for GM animal applications. Such monitoring may include quite complex approaches, e.g. to address health related assessment endpoints (see e.g. James et al. 2012). Furthermore for the assessment of adverse effects on biodiversity other approaches might be better suited (compare McGarvy 2007). McGarvey, D.J. (2007): Merging Precaution with Sound Science under the Endangered Species Act. BioScience 57/1, 65-70. James S., Simmons C.P., James, A.A. (2011): Mosquito Trials. Science 334, 771–772.

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28	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	4881 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
29	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	5. Post-Market Environmental Monitoring plan	This chapter summarises in a very general way the requirements for post-market environmental monitoring (PMEM) of GM animal applications according to the Directive 2001/18/EC. While this approach assures coherency with other guidance documents, e.g. PMEM guidance for GM plants (EFSA 2011), the guidance as included in the draft document needs to be further elaborated to address the specific monitoring needs of the different types of GM animal applications in appropriate detail. The draft guidance thus should state that the chapter is only providing gen-eral directions for applicants until further guidance is elaborated for the various types of GM animal applications. Lines 6413 – 6415: Pls. rephrase: "…applicants should then consider the appropriate post-market environmental risk management strategies and should describe how these are incorporated into the PMEM plan of the GM animal." The need for monitoring for GM animals seems to be evident against the background of the GM animal applications as developed currently and should not be up to deliberation at the side of the applicant. Line 6418: The expression "critical uncertainty" seems to be fully appropriate in itself; the current wording ("significant levels of critical uncertainty") introduces unnecessary complications. However, it should be taken into account that the level of critical uncertainty associated with an adverse effect needs to be determined with a view to the consequences for an adverse effect to be realized – with higher levels of risk possible the associated uncertainties need to be smaller to be "uncritical". Lines 6426 – 6430: It should be clearly stated that the applicant needs to submit the respective monitoring data to the competent Member States and EU institutions. Otherwise the EFSA recommendations that these data should be recorded in national and EU-level databases cannot be imple-mented.
30	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.3.5 Interactions of the GM mammals and birds with non-target organisms	Line 5521 & 5642: According to the glossary the term 'accessible ecosys-tems' defines biological systems within receiving environments to which the GM animals, including their by-products and the recombinant DNA, have access and with which they may interact. However this term is not discussed further in this draft guidance. Especially in case of semi-captive and non-captive GM animals the accessible environments may differ substantially. Moreover in different ecosystems the non-target organisms interaction takes place with also differs. For example the dominant prey exploited by a generalist may vary according to the ecosystem it lives in. This raises questions regarding the definition of and selection criteria for accessible environments used as a basis in the step-wise selection process for the identification of focal non-target organisms and the differentiation of various accessible ecosystems from another. The draft guidance should request the notifier to clearly define the accessible ecosystems considered in the era for potential effects on non-target organisms and to provide a justification for those accessible ecosystems not being considered in the selection of focal non-target organisms. Line 5673: TYPO: The substantive is missing in the first half of the sentence. The sentence should start with 'If this is the case,…'. Line 5776, 5782, 5784, 5785 & 5836: References are made to Table 2, but in fact Table 7 should be referenced. Line 6198: TYPO: In this sentence the words 'Guidance Document' is missing. The sentence should read: '…in the EFSA Guidance Document on the risk assessment for food and feed…'. Line 6220: TYPO: In this sentence the verb is incomplete. Possible phrasings would be 'due attention ought to be given', 'due attention should be given' or 'due attention is to be given'.
31	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	4875 ff.: Cf. comment on chapter 4.3. about mitigating measures.

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32	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	4803-4810: Reference to the EU Biodiversity Strategy in terms of genetic diversity is acknowledged.
33	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.3.4 Interactions of the GM mammals and birds with target organisms	Line 5380 & 5381: The Avian Influenza resistant chicken is not an example of a pathogen, but an example of a GM animal with a pathogen as target organism. The respective sentence should therefore read as follows: 'One example for a GM animal with a pathogen as target organism is the Avian Influenza resistant chicken, which…'. Likewise the mastitis-resistant cattle is not a pathogen, but a GM animal with a pathogen as target organism.
34	Federal Agency for Nature Conservation	DEU	4.3.2 Vertical and horizontal gene transfer	4786 ff.: Although a rational is given on why vertical gene transfer is discussed in this chapter, in order to avoid confusion it would be preferable if the potential loss in genetic diversity through artificial selection was discussed as part of chapter 4.3.1. As a consequence, chapter 4.3.1 should be renamed "Persistence and invasiveness, including vertical gene transfer". This would be in accordance with the respective chapters of 4.1.1 and 4.2.1. (cf. comments on 1862). Furthermore, an assessment of the loss of genetic diversity through artificial selection might also be applicable to GM fish and GM insects. A corresponding chapter should be included in the respective assessment parts (cf. comments on chapter 4.1.).
35	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.3.3 Pathogens, infections and diseases	Lines 5143, 5149, 5169, 5178, 5185, 5203: 'Risk pathway' is a term not commonly used in the terminology of environmental risk assessment (E-RA). Sometimes the term 'hazard identification' is being used for step 1 in risk assessment methodology, but subject to confusion with 'hazard characterization' (step 2). Therefore we recommend to use terminology common in GMO risk assessment, in this case 'problem formulation' (step 1) (EFSA 2010). As the respective chapter of the present draft guidance deals with step 1(i.e. problem formulation), the potential problems listed and described should be named 'problems' instead of 'hazards'. Instead of 'risk pathway' the term 'risk scenario' may be used. Line 5148-5165: This paragraph deals with the problem of the emergence of increased virulence as a consequence of the genetic modification for in-creased resistance. The respective headline however is misleading as it reads "evolution and emergence of increased resistance". Therefore the headline should, be corrected to 'evolution and emergence of increased virulence'. Line 5199 & 5200: For a better understanding the sentence should read: Note that regarding this hazard those aspects concerning pathogens and diseases are dealt with in this section, whilst those aspects concerning the change of microflora will be further dealt with in section 4.3.5. EFSA (2010). "Guidance of the GMO Panel on the environmental risk as-sessment of genetically modified plants." The EFSA Journal 8(11):1879: 1-111.
36	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	4772 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
37	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	4744 ff.: Cf. comment on chapter 4.3. about mitigating measures.
38	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	4493-4495: Consider as well that species intrinsic traits, which are relevant for persistence and invasiveness, may be altered unintentionally upon genetic modification, even if there is no obvious potential influence of the transgenic trait itself. In this respect basic direct data, generated by the applicants during the development of the specific GM animal, are required which enable characterisation of the GM animal and the identification of biological and ecological differences between them and their non-GM comparators (cf. comment on 593 ff.). These data must not be exclusively replaced by scientific literature as allowed in lines 4505-4507. 4510-4511: Cf. comment on 1932-1933.
39	Umweltbundesamt on behalf of Austrian Ministry	AUT	Step 2: Hazard characterisation	Line 4985: TYPO: Instead of "similar to the those introduced" the sentence should read "similar to those introduced".

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	of Health			
40	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.3.1 Persistence and invasiveness of GM mammals and birds and vertical gene transfer to wild and feral relatives	Line 4532: In this sentence the use of the term 'GM parental species' is unclear. If the term is supposed to refer to the recipient organism, which was used for transformation, then the prefix 'GM' used here is inadequate. Then the term 'parental organism' or 'parental line' (if focus is to be put on the use of the respective breeding line) should be used. If the term refers to GM species, which may produce offspring and thus become GM parental species, the sentence does not make sense as the rec-ommendation to use data from the recipient organism instead of data from taxonomic and ecological niche-surrogate non-GM species would be more logical. It is hard to imagine that absolutely no direct information on the recipi-ent/parental species is available, as the respective sentence suggests.. In any case the notifier needs to present the data according to Directive 2001/18/EC, Annex III A, for the parental and the modified organism respectively– either from available sources or by generation of the respective data by the notifier himself. On a case-by case basis further information valuable for the ERA may be obtained from the consideration of non-GM surrogates. In order to avoid confusion regarding the special case where no individual of the species, for which the application is made, is present in the receiving environment reference should be made to chapter 3.3., where the consequences of this fact for the comparative approach are being discussed. I this particular case the Draft Guidance Document for instance suggests considering the GM animal an alien species and evaluating the total environmental impact of the GM animal (see lines 904ff). Reference should be made to the evaluation of respective assessment approaches for alien invasive species (among others e.g. Essl et al. 2011, Verbrugge et al. 2010, Lonsdale 2011). In addition the uncertainties associated with such assessments (see e.g. McGeoch et al. 2012) need to be taken into account. Essl F., Nehring S., Klingenstein F., Milasowszky N., Christelle Nowack C., Rabitsch W. (2011): Review of risk assessment systems of IAS in Europe and introducing the German–Austrian Black List Information System (GABLIS). Journal for Nature Conservation 19, 339–350. Lonsdale W.M. (2011): Risk assessment and priorisation. In: Simberloff D. & Rejmánek M. (Eds.): Encyclopedia of Biological Invasions, Berkeley and Los Angeles: University of California Press. McGeoch M.A., Spear D., Kleynhans E. J., Marais E. (2012): Uncertainty in invasive alien species listing. Ecological Applications, 22(3), 959–971. Verbrugge L.N.H., Leuven R.S.E.W., van der Velde G. (2010): Evaluation of international risk assessment protocols for exotic species. Reports Environmental Science Nr. 352, Institute for Water and Wetland Research, Radboud University Nijmegen, The Netherlands.
41	Federal Agency for Nature Conservation	DEU	4.3.1 Persistence and invasiveness of GM mammals and birds and vertical gene transfer to wild and feral relatives	It is highly appreciated that the draft recommends that GM taxa should not be allowed to persist and become invasive pests in the wild. However it is not comprehensible that this statement only refers to mammals and birds and not to GM fish. The draft is not clear about the use of experimental data generated by the applicant. Experimental data are appreciated and shall be included when available (4505-4507), but may be replaced by literature data (e.g. 4505-4507 and 4522-4523) and are nowhere be regarded obligatory. This is neither case-specific nor in line with the step by step principle (cf. comment on 1226-1237). Please clarify which experimental data are mandatory and point to the step by step principle when encouraging applicants to perform experiments (lines 4681-4684. (cf. also comment on 320-325).The difficulty of release experiments is acknowledged but caged experiments giving insights into the comparability in phenotypic characteristics including behavioural aspects are possible without special environmental risks.
42	Federal Agency for Nature Conservation	DEU	4.3 Specific areas of risk for the ERA of GM mammals and birds	It is not sufficient for applicants to evaluate the efficacy and reliability of any mitigating measure. Instead it should be demonstrated that the proposed measures are practical and feasible to reduce exposure and risk, that they work efficiently and reliably under relevant rearing conditions and in relevant receiving environments in order to assess the overall risk. This requirement applies to other subchapters of 4.3. dealing with step 5: risk management strategies as well, namely 4744 ff., 4875 ff., 5024 ff., 5340 ff., 5480 ff., 5985 ff., 6075 ff., 6186 ff. and 6380 ff. 4432 ff.: Consider not just the GM animal, but its associated by-products, such as waste, manure etc. as well. This applies also to Table 5.
43	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.2.6 Impact on Human Health	Lines 4162-6165: The Draft Guidance Document states that "Applicants should consider both immediate and delayed effects on human health resulting from potential direct and indirect interactions with GM insects. This includes the risks for workers working with, and members of the public coming into contact with GM insects"

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				However several issue according to this objective are not sufficiently dis-cussed: Indirect health effects due to altered transmission patterns, e.g. by other vector species present in specific environments and impacts on the evolution of pathogens and disease agents are not adequately taken into account. Furthermore the possibility that food products can be contaminated by remains of dead larvae/pupae from GM animals, which are modified to express traits conferring conditional lethality acting late in offspring development (e.g. GM Olive fruit fly with female-specific lethality, Ant et al. 2012). With continous release programs of such GM animals an ongoing contamination of food products and potential ingestion of material derived from GM animals is possible and should be considered in the the Draft Guidance Document. Ant T, Koukidou M, Rempoulakis P, Gong HF, Economopoulos A, Vontas J, Alphey L (2012) Control of the olive fruit fly using genetics-enhanced sterile insect technique. BMC Biol., 10, 51.
44	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.2.4 Interactions of the GM insect with non-target organisms	General comment: Pathogens and disease agents should be considered as NTOs and adequately considered. Even if modified for other aims than reducing their vectoring capacity, many GM insects that could be potentially released are from species, which are known to transmitting pathogens and disease agents. Thus a detailed assessment of impacts on these organisms/agents should be required for applications of such GM insects.
45	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	4347 ff.: Cf. comment on chapter 4.2. about mitigating measures.
46	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.2.3 Interactions of the GM insects with target organisms	Line 3310ff: The definition of target organism (TO) should be revised and clarified. On the one hand non-GM populations of the same species are targeted, which should not called “organism” to avoid confusion. At the other hand GM insects with reduced vectoring capacity target other TOs namely the respective pathogen species.
47	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	4347 ff.: Cf. comment on chapter 4.2. about mitigating measures.
48	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	4181: It is not comprehensible why data on specific toxicity testing are not recommended within the framework of this guidance. Toxic proteins or other toxic compounds may not only be toxic for humans but also for other mammals (wildlife or husbandry). Please explain. 4198-4204: In addition this section should address species shifts and their role in the transmission of diseases (in the case of GM mosquitoes also non-target diseases).
49	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.2.1 Persistence and invasiveness, including vertical gene transfer	General comment: The aspect of incomplete penetrance of traits for conditional-lethality as regards dispersal of this and coupled marker traits needs to be considered. Line 2981: Current applications mostly aim at early- or late-acting conditional lethality or reducing mating efficiency (e.g. by the flightless-trait conferred to offspring-females). The differences of these applications to sterile insects incapable of producing offspring, e.g. sterile insects used in SIT-programmes need to be discussed and considered. Line 2995: Novel traits like insecticide-resistance or resistance towards diseases (see Beech et al 2012) should be mentioned, since they are enhancing fitness under specific conditions. Line 3089ff: Specific measures to avoid release into unintended environ-ments during rearing and transport should be considered like for SIT-applications. Beech CJ, Koukidou M, Morrison NI, Alphey L (2012) Genetically Modified Insects: Science, Use, Status and Regulation. Collection of Biosafety Re-views 6 : 66-124. http://www.icgeb.org/~bsafesrv/pdffiles/Col6_Beech.pdf

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50	Federal Agency for Nature Conservation	DEU	4.2.6 Impact on Human Health	The different aspects regarding human health also apply to animal health (especially wildlife mammals and husbandry). 4161: The assessment should not focus on new hazards, but generally on hazards by the GM insect. 4162: “whether the GM insects pose a new hazard for ….”. We suggest broadening the scope and not only focusing on the identification of new hazards. Instead the risk assessment should consider any hazard related to intended and unintended changes in the fitness, life-history or behaviour of the GM insect which may directly or indirectly affect human and animal health. As ecological interactions between hosts and pathogens (including transmission) can be highly complex hazards must be identified which result of interactions between different vectors and diseases.
51	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.2 Specific areas of risk for the ERA of GM insects	General comment: Other arthropod species than insects are currently ge-netically modified and may be relevant as regards ERA in the medium-term. Some of the considerations presented in this Draft Guidance Document . Line 2949-2950: Spraying chemical insecticides, which is a focal issue of public health concerns, is just one of the management measures for disease vectoring insects, like mosquitoes. Other means are based on treated bed-nets, use of bacteria and funghi to kill mosquitoes and management of breeding sites (see e.g. Gravitz 2012). This should be mentioned for completeness as the risks of alternative management measures may be relevant for ERA of GM insects. Gravitz L. (2012): The last bite. Nature 484, S26-27.
52	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	4149 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
53	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	4135 ff.: Cf. comment on chapter 4.2. about mitigating measures.
54	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	4034 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
55	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.1.4 Pathogens, infections and diseases	Line 2556: "...stringent biosafety measures can be implemented...": As the aim is to prevent pathogens from spreading the sentence should read "...measures should be implemented..."
56	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.1.3 Impacts on biotic components and processes	Line 2221: correct reference: "Directive 2001/18/EC" and not "EC2001/18".
57	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	4034 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
58	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.1.2 Horizontal gene transfer	Line 2188, page 55: The reference given (Rizzi et a. 2011) is not included in the reference list at the end of the document. The reference listed is Rizzi et al. 2012 and deals with DNA degradation in the mammalian gastrointestinal tract. This should not be referenced to substantiate statements regarding DNA degradation in the fish gut.
59	Federal Agency for Nature	DEU	Step 5: Risk management	4013 ff.: Cf. comment on chapter 4.2. about mitigating measures.

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	Conservation		strategies	
60	Federal Agency for Nature Conservation	DEU	Step 2: Hazard characterisation	3881-3886: In terms of focal species we suggest to relate here to the experience gained with the risk assessment of biological control agents described in Bigler et al. (2006). Bigler, F., Babendreier, D., and Kuhlmann, U. 2006. Environmental impact of invertebrates for biological control of arthropods. 2006. CABI Publishing. 3900-3905: For the impact on other species any derivation from life-history parameter is important. It will be also necessary to gain direct data on the competitive abilities of the GM insects in comparison to the comparator.
61	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	4.1.1 Gene transfer and consequences	Figure 6: The questions in the decision tree always start "Will GM fish...". This proposes a 100% certainty that if the question is answered with no, the described event will not happen. In fact it only states that the event is not intended. In line 1899 to 1905 on page 48 the expression "can the GM fish..." is used. This should also be used in the figure, as it reflects much better the intention of a decision tree. As an example the starting question reads "Will the GM fish escape and survive outside the rearing system?" As an escape is never intended, and happens accidentally, this question could never be answered with "no", except the GM fish is reared in a 100% closed system, which is unlikely or if the authorization is for import of dead fish only. It seems that basically all other questions of the decision tree can only an-swered "yes" or "no" with a high probability only after comprehensive studies. These studies need to be case specific (trait and species and their combination) and depend highly on the intended management system. Therefore also the term "basic information" used in line 1899 is slightly misleading. In any case it is an absolute necessity to thoroughly justify and support this justification with scientific data if any question of this decision tree is an-swered "no" and therefore the ERA does not consider this issue. Line 1929 ff: It is suggested that data generated for GM fish with the same trait or similar transformation events may be used to justify the scope of the ERA. According to Dir. 2001/18/EC the ERA should always be case specific. This is especially important for the problem formulation step. If data from other GM events are used this needs to be thoroughly justified, not only if the respective data were generated outside the EU. This needs to be reflected in this paragraph.
62	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	3700-3703: It is appreciated that the draft notes that the lists of examples provided as potential adverse effects on NTOs are non-exhaustive. In terms of possible interactions to be considered by the applicant the draft suggests possible interactions based on different factors including particularities of the GM insect, traits, receiving environment, but missing to mention the genetic modification which should be added. 3724: Replace will by may in “Following suppression and preventative releases, GM insects will be present only for a limited time and in a limited area.”
63	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	3.7 Uncertainty analysis	General comment: The results of a Working Group discussion concerning “Managing uncertainty and variability” at the conference “Prudent Precau-tion? Experiences with the Precautionary Principle 2000-2010”, European Environment Agency, 2.-3. September 2010, should be taken into account for revision of the draft chapter, see http://www.umweltbundesamt.at/fileadmin/site/umweltthemen/gentechnik/EAA-PP-Sept2010/WG_reports_EEA-Sept2010.pdf Line 1735: The expression “critical uncertainty” seems to be fully appropriate in itself; the current wording (“significant levels of critical uncertainty”) introduces unnecessary complications.
64	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	3.6 Long-term effects	Lines 1438-1444: The above comments to Chapter 3.3. relating aspects as regards alien species should be considered also for this chapter. Lines 1462-1465: Some GM animal applications substantially differ from GM plant applications (which are discussed in the cited reference), since they are deliberately developed to long-term population replacement of non-modified animals, like mosquitoes, in urban, rural and possibly

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				unmanaged environments. While the chapter should stress that the assessment of long-term effects for ERA needs to be conducted during ERA anyway, it should state that assessment of long-term effects must be considered a focal issue for these applications! It may also be necessary to revise the categorization given in Lines 1466-1474 to indicate this aspect adequately. Lines 1513-1515: Add: Data, experiences and standards derived from comparable applications using non-GM animals if available, like sterile insect technique (SIT) applications used for arthropod control. Lines 1522-1526: Modelling approaches should be validated with existing data and should reflect realistic scenarios. If differing assumptions can be made alternative models need to be established for comparison. Lines 1547-1548: Potential indirect long term effects due to behavioral changes of the human community, e.g. as regards disease vectoring animals like mosquitoes, which are relevant if the efficacy of transmission-reducing GM traits is lost should be considered as well and monitoring of such aspects should be required.
65	Federal Agency for Nature Conservation	DEU	4.2.4 Interactions of the GM insect with non-target organisms	3679 ff.: According to these lines the potential impact on ecosystem services and ecological functions provided by NTOs, as well as species of conservation concern should be considered as well. This includes biological control as well. However, this issue is underrepresented within the draft document. Therefore, please mention biological control organisms here separately.
66	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	3.4 The use of non-GM surrogates	General comment: It should be stressed that the use of non-GM surrogates for experimental studies involving release needs to be based on an adequate understanding of the adverse effects of such releases. The guidance on GM animals which is being developed may inform such considerations.
67	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	3655 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
68	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	3626 ff.: Cf. comment on chapter 4.2. about mitigating measures.
69	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	3389-3396: Suggest shifting this paragraph to chapter 4.3.9. Impact on human health. 3397: Add host range and breeding site selection to measurement endpoints. 3452-3455: Add a cross reference here to chapter 3.7.3. Interplay between ERA conclusions and PMEM.
70	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	3.3 Choice of comparators	General comments: The above mentioned comments to Chapter 2 should also be taken into account for revision of this chapter. Comparison should not only be made between the GM animal and its non-GM counterpart, but also between ecological effects of the intended or unintended release and its characteristics on the environment and health and other possible management measures, if available! Lines 904-924 partly acknowledge this and the conclusions therein are strongly supported! However, e.g. concerning population control applications, a full comparison, cannot be focused on the GM animal alone, but needs to take into account all effects associated with the management system based on a specific GM animal (e.g. any necessary pre-release treatment with insecticides to ensure efficacy of a GM insect release). For some GM animals, e.g. from pest species or disease vectoring species a direct comparison with releases of non-GM counterparts may not be possible at all or only limited comparability (e.g. to non-GM sterile animal releases) may exist. A sub-chapter on GM mammals and birds is missing!

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				Lines 904-908: The relevance of all regulations applying to introduction of alien species needs to be stressed throughout the document as regards the proposed release of GM animals! The available experience with the risk assessment of (invasive) alien species should be considered and referenced in the Draft Guidance Document. Reference should be made to the evaluation of respective approaches for assessment of invasive alien species (among others e.g. Essl et al. 2011, Verbrugge et al. 2010, Lonsdale 2011). In addition the uncertainties associated with such assessments (see e.g. McGeoch et al. 2012) need to be taken into account. Lines 940-942: Information should be required on differences of the GM progenitor line and the chosen comparator(s) as regards issues which are relevant for ERA, e.g. vectoring capacity for pests and diseases, resistance to environmental factors and potential management measures, e.g. pesticide susceptibility, etc. Essl F., Nehring S., Klingenstein F., Milasowszky N., Christelle Nowack C., Rabitsch W. (2011): Review of risk assessment systems of IAS in Europe and introducing the German–Austrian Black List Information System (GABLIS). Journal for Nature Conservation 19, 339–350. Lonsdale W.M. (2011): Risk assessment and priorisation. In: Simberloff D. & Rejmánek M. (Eds.): Encyclopedia of Biological Invasions, Berkeley and Los Angeles: University of California Press. McGeoch M.A., Spear D., Kleynhans E. J., Marais E. (2012): Uncertainty in invasive alien species listing. Ecological Applications, 22(3), 959–971. Verbrugge L.N.H., Leuven R.S.E.W., van der Velde G. (2010): Evaluation of international risk assessment protocols for exotic species. Reports Environmental Science Nr. 352, , Institute for Water and Wetland Research, Radboud University Nijmegen, The Netherlands.
71	Federal Agency for Nature Conservation	DEU	4.2.3 Interactions of the GM insects with target organisms	3316: Replace “many of which are likely” by “which may”. 3319ff: If this refers to the use of new varieties as a replacement strategy with domesticated plants this is hardly possible to compare. Please explain in more detail.
72	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	3286 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants. 3291-3295: This paragraph repeats information more exhaustively and more carefully formulated in the problem formulation and is out of place in this step. The paragraph should be deleted. 3297: The risk potential of unintended horizontal mobility should be considered for the recombinant DNA in general and not be limited to recombinant DNA containing autonomous transposons (it is assumed as it is not clarified in the text), gene drive systems or relevant sequence similarity to microbes. The restriction should be removed from the text. 3298: This sentence is a repeat of the content stated in the first paragraph of the overall risk evaluation and can be deleted.
73	European Beekeeping Coordination	BEL	4.2 Specific areas of risk for the ERA of GM insects	1. Too general and vague guidelines, saying nothing about how risk assessment should be carried out. There seems to be a lack of competence in the EFSA so far for the definition of guidance for the evaluation of GM insects. One could wonder: if there is this lack of competence in the definition of risk assessment methodologies, how is the RA in practice going to be implemented? It would be recommendable to precisely describe the tests to be done to prove both hazard and exposure. 2.Given the different areas of competence included for the risk assessment of GM animals (environment, health, socio/economic issues, etc) multidisciplinary teams from different EU agencies should be created to profit from their respective field of expertise. 3. It is somehow bizarre that EFSA is commenting on risk management. The role of the EFSA is risk assessment: problem definition, hazard and exposure characterization and risk characterization. Risk management is not the role of the applicant, but of the risk managers (Commission and Member States). Applicants might be consulted and they might provide their advice, but they are not the ones deciding risk mitigation measures.

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				4. GM animals for which reproduction cannot be 100% controlled pose per se an unacceptable risk. Therefore, methodologies need to be proposed to show that no vertical transfer of GM genes exist. Specific methodologies should be described for evaluating the impact of a substitution of species in a certain ecological niche. Currently, they are not defined in the GD. Neither are described methodologies to evaluate socio-economic impact of the introduction of GM insects for which non-GM counterparts exist in Europe. Reproduction could happen between both organisms. Companies liberating GM insects could claim that local non-GM insects are benefiting from their technology. Bees are very good examples of this. Beekeepers could be sued by companies producing GM bees for appropriating without permission from the advantages their products have introduced. These kind of assessment should as well be included in risk assessment. 5. Risk assessment must have a more holistic approach, including all pros and cons, together with alternatives to the GMs under evaluation. E.g. in the future GM bees could be produced to increase pollination by increasing their resistance to insecticides. This would lead, as it has happened with the Roundup Soy, to the great increase in the use of insecticides on the trees that require pollination. The devastating impact on biodiversity and potential contamination of the environment is clear, only leaving GM bees alive. Risk assessment needs to incorporate a much more holistic approach. 6. Risk assessment of GM animals, same as that of GM plants or pesticides, should be per se a consultative process. 7. Why does the applicant have the right to decide if the risk that its products pose to environment, health (human or animal), or to the socio/economical situation is acceptable or not, or to compare the risk with the positive effects the company is claiming for the GM animal? (lines 552-554 or lines 4092-4093) Introducing risk in the environment when they are unnecessary (because other alternatives exist and should be taken into account in risk assessment) goes against the precautionary principle. It is unacceptable.
74	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	3.2 Experimental environment	Lines 793ff: The association of animals with (human) pathogens and dis-ease agents should be mentioned, which is adding further complexity and needs to be fully considered for ERA!
75	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	3281 ff.: Cf. comment on chapter 4.2. about mitigating measures.
76	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	3.1 Receiving environments	General comment: For selection of relevant receiving environment any predictable changes in EU environments, e.g. according to climate change or other human interventions, should be taken into account. Lines 642: Include: "…, their potential for being unintentionally released and spread, …" Lines 699-703: "Interactions with humans" should be included in the sentence and in the following considerations. Lines 737ff: Revise to indicate that the recommended studies should not result in a release of GM animals which might have adverse effects e.g. on certain non-target organisms or human beings in areas where such risks may manifest themselves! Line 762-763: The presence of other GMOs (not just other GM animals) should be taken into account.
77	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	3110: The problem formulation provides the applicant with a detailed, but not exhaustive, list of points to consider. The division of the two potential HGT pathways (to other insects and to microorganisms) and separate discussion is recommendable and prevents confusion. 3172: The guidance document states that one of the biological factors to be considered is the presence of a plausible mechanism that facilitates horizontal transfer at a biologically relevant frequency. This is certainly true and should be considered, but it should be kept in mind that the mechanisms facilitating horizontal transfers between insects is unknown (Silva et al., 2004). Thus the absence of an obvious (and known) transfer mechanism is not a criterion for the discontinuation of the assessment. The lack of scientific knowledge on this subject should be indicated. Silva JC, Loreto EL and Clark JB, 2004. Factors that affect the horizontal transfer of transposable elements. Curr. Issues Mol. Biol. 6, 57-72.

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				3190: The guidance document recommends that fitness changes conferred by the recombinant DNA should be considered as they could lead to positive selection and long-term establishment. Potential fitness advantages conferred by the transgene should certainly be considered. But it should be kept in mind that transferred genes could take on new functions or have more than one function and would thus be subjected to unexpected selection pressure. 3205: It is stated that only natural transformation is known to facilitate uptake and genomic integration of DNA fragments. This is not entirely correct. DNA fragments can also be transferred by transduction or conjugation. Free DNA fragments on the other hand can only be incorporated via transformation. Thus the statement should be clarified by the addition of "free" to "DNA fragments". For clarification it should also be explained why the other processes by which exogenous genetic material may be introduced into a bacterial cell are not considered. 3221: In order to identify microbial species that could serve as recipients for HGT, the ability of the microorganisms to develop competence should be considered. This is certainly a relevant factor, but it should be kept in mind that the ability to become competent has only been investigated for a very small portion of the known microorganisms. This uncertainty should be mentioned. 3240: The inclusion of the consideration of any positive selection conferred by the transferred trait is legitimate but does not consider the uncertainty that the transferred gene might be subjected to a different, not easily apparent, selection pressure due to a change of function. 3245: The fragment "in case the above conditions are met" should be deleted in light of the uncertainties and lack of knowledge concerning HGT from insects to microorganisms.
78	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	2.2 Information to identify potential unintended effects	Lines 569-572: It should be mentioned that for some species which are modified, e.g. pest species or species transmitting pathogens and diseases the comparison "under the same environmental conditions" may simply not be feasible, if this comparison necessitates an environmental release! Data can therefore be only generated under the more artificial conditions of confined testing. Lines 580-583: A targeted compositional analysis as referenced in this paragraph will not be fully sufficient to address the assessment of all GM animal applications, specifically the ones that are not developed for use as farm(ed) animals for food use. Further guidance to address this issue for GM animals specifically from non-food species taking into account the possibilities offered by new profiling techniques (Eckerstorfer et al 2012) should be developed. Eckerstorfer, M., Narendja, F., Roschko, R., Heissenberger, A., Gaugitsch, H. (2012): Gutachten zum Stand und zu den Möglichkeiten des Einsatzes von Omics-Technologien in der GVO-Bewertung. BfN-Skripten 313, Bonn, Germany; http://www.bfn.de/fileadmin/MDB/documents/service/Skript_313_komplet_barrierefrei.pdf
79	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	2.1 Different steps of the Environmental Risk Assessment	Lines 327-329: The objective according to Directive 2001/18/EC should be referred to: "to address direct and indirect, immediate or delayed (including cumulative long-term effects) adverse effects on the environment and human and animal health" This should be taken into account throughout the whole Draft Guidance Document. Table 1: Although the table indicates that only examples are listed, it should be revised for increased completeness and relevance. Lines 363ff: The wording should be revised to reflect the above Comments to Chapter 2. The characteristics of the GM animal and the characteristics of their intended or unintended release need to be assessed! It is also important that all affected characteristics of exposed environments and ecosystems are taken into account. To stress that indirect effects need to be addressed adequately the term "exposure pathway" should be replaced by more adequate wording. Lines 418ff: Considerations outlined in Directive 2001/18/EC Annex 2 Sec. D.1. should be referred to as a starting point for problem formulation and the indicated list revised to better address these objectives. Lines 517-519: In addition it needs to be mentioned that the indirect risks of GM animal characteristics such as reduced reproductive capacity or infertility, which are considered to facilitate risk management, need to be fully assessed!

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80	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	3093 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
81	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	3089 ff.: Cf. comment on chapter 4.2. about mitigating measures.
82	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	2. Strategies for the ERA of GM animals	Lines 298ff: It is acknowledged that the paragraph on the principles which shall be applied for ERA states that an explicit uncertainty analysis needs to be conducted. However it should be explicitly stated that the results of this uncertainty analysis need to be adequately discussed in the ERA conclusions. Lines 302ff: The Draft Guidance Document also indicates that the comparative approach is a key element for the approach to design ERA for GM animals. However the way how this approach is described is too simplistic and should be revised. The guidance needs to acknowledge that a comparison of the characteristics of a specific GM animal to its conventional counterpart as indicated in Lines 309-311 is necessary but not sufficient to assess all potential applications of GM animals. This approach is insufficient specifically for the following groups of GM animal applications: applications directed to objectives like population suppression and population replacement of pest species or species transmitting pathogens and diseases; applications of GM animals which may result in the accidental or unavoidable release of GM animals that will persist in the environment. The latter applications may cause adverse effects on endemic populations of their own or other species or affect ecosystem characteristics or stability. For a comprehensive comparative approach therefore adverse effects of the release (programmes) of GM animals on ecosystem dynamics need to be assessed to complement the comparison described in Lines 309-311. Comparison of the environmental and health risks should be made with the adverse effects of other management approaches, e.g. management with pesticides, non-GM based sterile animal releases, or any other interventions towards the objective which is addressed by the specific GM animal application. Such an approach is partly but not fully acknowledged by Chapter 2.2 (Lines 589-592) and Chapter 3.3. A respective change of wording is also necessary throughout Chapter 2.1.
83	Federal Agency for Nature Conservation	DEU	Step 2: Hazard characterisation	3040-3041: Please add here “and characterise non-transformed insects, their ecological niches and functions.”
84	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	1. Scope of this Guidance Document	Lines 248-250: The Draft Guidance Document addresses specifically the “… commercial release of GM animals into the environment but excludes their release for experimental purposes under Part B of Directive 2001/18/EC”. The guidance should better reflect that commercial as well as non-commercial releases, e.g. of specific GM arthropods may be possible (comp. Benedikt et al. 2010). Further the delineation of experimental vs. “commercial”, unconfined releases is difficult, e.g. with the release of GM insects that are not strictly self-limiting as regards their reproductive capacity (i.e. not sterile and with comparable fitness than related non-GM animals). Lines 257-258: The argument “likely to be transformed” also applies to crustaceans and mites, e.g. arthropod groups other than insects (Benedikt et al. 2010), as well as certain mollusks and amphibians and would not be indicative of the identified animal groups for consideration. Benedict M., Eckerstorfer M., Franz G., Gaugitsch H., Greiter A., Heissen-berger A., Knols B., Kumschick S, Nentwig W. & Rabitsch W. (2010): Defi-ning Environmental Risk Assessment Criteria for Genetically Modified In-sects to be placed on the EU Market. External Report for EFSA. http://www.efsa.europa.eu/en/scdocs/scdoc/71e.htm
85	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	3002-3003: Rewording suggested: “loss of endangered or ecological valued species” instead of “loss of valued ecological species”. 3004-3010: Failure may also happen when the sterile insects take up the gene activating agents (e.g. antibiotic needed to activate the genes rendering the organism fertile again) from the environment. 3031: We suggest to explain „genetic drive system“ either by a reference or by taking the term into the glossary.

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86	Federal Agency for Nature Conservation	DEU	4.2 Specific areas of risk for the ERA of GM insects	Many of the potential hazards identified focus on effects mediated by insect fitness or behaviour. We suggest that ecology and life-history of the GM insect should be included in all instances. Both aspects are needed to estimate effects on the population dynamics of species (including density dependence) and to understand possible changes in the receiving ecosystems. It is not sufficient for applicants to evaluate the efficacy and reliability of any mitigating measure. Instead it should be demonstrated that the proposed measures are practical and feasible to reduce exposure and risk, that they work efficiently and reliably under relevant rearing conditions and in relevant receiving environments in order to assess the overall risk. As a proof-of-concept this requirement applies especially to the Sterile Insect Technique (SIT) and to all subchapters of 4.2. dealing with step 5: risk management strategies as well, namely 3089 ff., 3281 ff., 3626 ff., 4013 ff., 4135 ff. and 4347. 2940-2944: The first part of the paragraph may serve as baseline, against which the use of GM insects may be compared. To give the complete picture we suggest referring also to the concept of integrated pest management and biological control. 2949: Please add after chemical insecticides “and mechanical mitigation measures (e.g. mosquito nets)” 2969: Because the lack of knowledge about the outcome of gene flow to related species it can be used as an indicator pointing to the development of possible problems. The used wording seems to be too restrictive.
87	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	2931 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
88	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	2928 ff.: Cf. comment on chapter 4.1. about mitigating measures.
89	Federal Agency for Nature Conservation	DEU	Step 2: Hazard characterisation	2862-2863: Please specify that relevant rearing conditions shall be considered for pathogen profiling such as overcrowding, feed compositions, growth rates, medication etc.
90	Center for Food Safety	USA	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Figure 6. Problem Formation Questions. begins with the question: Will GM fish be released or escape and survive outside rearing systems? If the answer to this question is no, then the risk assessment is to be confined to the impacts of GM fish in managed systems. This could allow far too limited risk assessments. Most aquaculture systems need to be near major water sources. Few really recycle their water adequately to locate far from a cheap water source. The need to locate near a water source means that these facilities are near major tributaries of rivers or near estuaries. These are extremely flood prone environments, so flood prone that all risk assessments should assume that at some point the GM fish will escape. Some proponents of GM fish culture (notably the AquaBounty company) argue that their GM fish will only be grown in inland tanks, but these tanks will necessarily be located near major tributaries and even the experimental grow out tanks that the company was leasing in Panama flooded. Moreover, there are no legal requirements that GM fish only be raised in inland tanks and for salmon in particular, a vast majority of salmon farming around the globe occurs in open ocean net facilities. It must be assumed that GM fish will eventually be produced in ocean facilities and in turn will ultimately escape into the wild.

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91	Umweltbundesamt on behalf of Austrian Ministry of Health	AUT	Abstract	General Comments to the whole document: We appreciate the Draft Guidance Document at hands as an initial effort to establish guidance on the environmental risk assessment (ERA) of GM animals and to complement other guidance documents by EFSA. The Draft Guidance Document tries to address all issues associated with the environmental risk assessment of GM animals in a single document using a common structure. This is associated with a number of problems, e.g. (1) the document itself is quite voluminous, yet far from being compre-hensive – see e.g. the below comments to Chapter 5 on PMEM, (2) the scope is contradictory – the guidance should address all GM animals to be released into the environment and placed on the EU market according to Regulation (EC) No. 1829/2003 or Directive 2001/18/EC, yet only GM fish, GM mammals and birds and GM insects are discussed in detail, other GM animals which would deserve attention (e.g. other GM arthropods, molluscs or amphibians) are not considered specifically, (3) different types of GM animal applications are subjected to a uniform ap-proach, e.g. replacement of non-GM farm(ed) animals with GM-animals of the same species, release of GM animals from species that are either non-domesticated and/or alien and/or invasive, use of GM animals for farming purposes as well as for completely other purposes, like population replace-ment or suppression. However the different issues associated with these applications would need a more specific discussion and approach, also as regards the respective cross-cutting considerations, (4) different types of release scenarios are treated with a uniform ap-proach, e.g. the placing on the market of GM animals by commercial applicants opposed to release of GM animals for public, plant or animal health reasons by international or national institutions in the frame of e.g. wide-area, long duration release programmes, that may additionally involve non-EU countries. However transboundary movements are not addressed in the Draft Guidance Document. The problems created by the issues mentioned above are difficult to address in a single document. The Draft Guidance Document therefore should be revised considering the above issues and further guidance should be developed for issues that cannot be possibly addressed comprehensively in a general guidance document. For example the issue of PMEM for GM animals would require a more elaborate separate guidance document. Other aspects should be addressed in more depth in the Draft Guidance Document at hands. E.g. impacts on non-GM animal health and welfare are only discussed in the Chapter on GM mammals and birds. Indirect health effects due to impacts of GM insects on the development of pathogens and disease agents and by impacts on other vector species present in certain environments are also not addressed sufficiently. It should also be explained, why animals producing pharmaceuticals are not addressed by the Draft Guidance Document and how adequate as-sessment of such applications will be conducted. The Draft Guidance Document should thus be checked for consistency, re-vised for clarity and elaborated to include necessary details on information required for risk assessment. The Draft Guidance Document should further indicate where further guidance is needed and/or forthcoming. A second round of consultation seems necessary to discuss the required revisions and will be appreciated.
92	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	2791ff: While lengthy elaborations are provided for major fish pathogens there is limited guidance on how applicants shall assess where there is an increased capacity from the GM fish to cause or transmit human diseases.
93	Federal Agency for Nature Conservation	DEU	4.1.7 Impact on human health	2770-2771: According to the draft applicants should provide information, specified in the Annex III of the Directive 2001/18/EC (EC, 2001), to evaluate whether the GM fish present a new hazard for human health compared with appropriate comparators and equally for GM insects (4161-4162), but not for GM animals and birds and not for impacts on other issues. This restriction, namely to refer to Annex III for certain groups of animals and for impacts on human health only, is according to our point of view not in line with recital (27) of Directive 2001/18/EC which sees the principles in Annex II and the information requirements in Annex III as basis for further specifications. Therefore, this guidance needs revision accordingly.

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94	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	2761 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
95	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	2754 ff.: Cf. comment on chapter 4.1. about mitigating measures.
96	Federal Agency for Nature Conservation	DEU	Step 2: Hazard characterisation	2740-2742: When assessing the efficacy of captivity measures for restricting or preventing escape of GM fish applicants should also refer to the practice and demonstrate to what extend their measures are suited to prevent incidents from the past including small scale escapes through perforated nets or large scale escapes through averages at bad weather or upon harvest. Regarding the possibility of retrieving escaped animals not only the efficacy should be assessed, but also whether it is possible and feasible.
97	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	2707-2730: The text is very general and provides some specific considerations for cold, anoxia or salt tolerant GM fish. It is more or at least equally obvious to mention increased growth rate of GM fish as an example. Please add this here and consider associated rearing and management conditions such as increased feed consumption, overcrowding, nutritional stress, altered hygiene measures and their environmental impacts.
98	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	2680 ff.: Cf. comment on chapter 4.1. about mitigating measures.
99	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	2551 ff.: Cf. comment on chapter 4.1. about mitigating measures.
100	Federal Agency for Nature Conservation	DEU	Step 2: Hazard characterisation	2497-2500: Please specify the required information 2506-2508: Please specify or suggest methods to determine changes in the production of metabolites.
101	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	2464-2465: According to the draft comparison between the GM fish and its conventional comparator should be performed under representative environmental conditions. Showing or demonstrating representativeness of environmental conditions is probably very challenging bearing in mind the several interacting factors listed in 2483ff which can influence disease resistance and immune response of fish including associated microorganisms and parasites in receiving environments (cf. 2521-2523). Therefore it is requested to perform the comparison under a range of all potential environmental conditions. Please clarify that environmental conditions relate to the range of environments into which the GM animal(s) and their by-products will be released or may escape or be distributed (cf. 648-650). Also, guidance is missing about the quality and quantity of required experimental data.
102	Federal Agency for Nature Conservation	DEU	4.1.4 Pathogens, infections and diseases	2409-2461: This introducing paragraph presents interesting considerations about traits of GM fish and their relation to infectious diseases. A cross reference is missing linking these considerations to the steps of the risk assessment on the following pages.
103	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	2343 ff.: Cf. comment on chapter 4.1. about mitigating measures.
104	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	2231-2233: We do not agree with the suggestion to examine only occasionally, whether the GM fish actively or passively secretes substances or if such can be released to the environment upon death of the GM fish or as metabolites. According to the draft applicants shall consider what effects metabolic by-products of other animals may have on a GM fish when it invades a new environment (2321-2324) and this should apply vice versa as well. Exudates are associated by-products of a GM animal and belong to the basic information required to characterise the GM fish and to identify biological differences between it and the conventional counterpart.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
105	Federal Agency for Nature Conservation	DEU	4.1.3 Impacts on biotic components and processes	This chapter raises a number of possible interactions of a GM fish with target and non-target organisms. However, guidance is missing about when experimental data are required to test certain hypotheses for risk assessment. Experiments in mesocoms (2281-2282) and models and scenario testing (2294-2296) are suggested, which is appreciated, but it is unclear in several other cases, whether the expressions: to determine (2293), to examine (2232), to assess (2241) or to study (2243) involve the collection of experimental data or not.
106	Federal Agency for Nature Conservation	DEU	Step 6: Overall risk evaluation and conclusions	2212 ff.: Please add: The risks and uncertainties described in the overall conclusions of the ERA provide the basis for the PMEM plan to be proposed by applicants.
107	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	2207 ff.: Cf. comment on chapter 4.1. about mitigating measures.
108	Federal Agency for Nature Conservation	DEU	Step 3: Exposure characterisation	2187-2189: The sentence is redundant and should be replaced with “Potential exposure routes to be considered are for example”. The following bullet points should include examples for possible exposure routes for the horizontal transfer from fish to other vertebrates. 2192: The citation of Rizzi et al. (2011) should be added to the references (or corrected to Rizzi et al. 2012 if this publication is meant). 2199: This bullet point is not an example for a potential exposure route and should be exempt from the list.
109	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	2090: In order to achieve better readability of the text and to avoid confusion, it might be advantageous to divide the problem formulation in subdivisions on the horizontal transfer between fishes and other eukaryotes and on the HGT to microorganisms similar to the structure of the problem formulation of chapter 4.2.2. 2099: The guidance document correctly states that HGT between higher eukaryotes are only infrequently observed. An interesting article describing a horizontal transfer between teleost fishes and lampreys, their vertebrate parasite, has recently been published (Kuraku et al., 2012). It would be helpful for the applicant to be referred to scientific literature on the topic of HGT between vertebrates. Thus the citation of Kuraku et al., 2012, should be added to the statement. Kuraku S, Qiu H and Meyer A. (2012). Horizontal transfer of Tc1 elements between teleost fishes and their vertebrate parasites, lampreys. Genome Biology and Evolution doi:10.1093/gbe/evs069. 2105: The guidance document states that one of the biological factors to be considered is the presence of a plausible mechanism that facilitates horizontal transfer at a biologically relevant frequency. This is certainly true and should be considered, but it should be kept in mind that the mechanisms facilitating horizontal transfers between vertebrates are unknown (Kuraku et al., 2012). Thus the absence of an obvious transfer mechanism is not a criterion for the discontinuation of the assessment. The lack of scientific knowledge on this subject should be indicated. Kuraku S, Qiu H and Meyer A. (2012). Horizontal transfer of Tc1 elements between teleost fishes and their vertebrate parasites, lampreys. Genome Biology and Evolution doi:10.1093/gbe/evs069. 2116: It is stated that only natural transformation is known to facilitate uptake and genomic integration of DNA fragments. This is not entirely correct. DNA fragments can also be transferred by transduction or conjugation. Free DNA fragments on the other hand can only be incorporated via transformation. Thus the statement should be clarified by the addition of “free” to “DNA fragments”. For clarification it should also be explained why the other processes by which exogenous genetic material may be introduced into a bacterial cell are not considered. 2137: In order to identify microbial species that could serve as recipients for HGT, the ability of the microorganisms to develop competence should be considered. This is certainly a relevant factor, but it should be kept in mind that the ability to become competent has only been investigated for a very small portion of the known microorganisms. This uncertainty should be mentioned. 2159: The inclusion of the consideration of any positive selection conferred by the transferred trait is legitimate but does not consider the uncertainty that the transferred gene might be subjected to a different, not easily apparent, selection pressure due to a change of function.

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110	Federal Agency for Nature Conservation	DEU	Step 5: Risk management strategies	2056 ff. Cf. comment on chapter 4.1. about mitigating measures.
111	Federal Agency for Nature Conservation	DEU	Step 3: Exposure characterisation	2004-2009: The likelihood of spread of the recombinant DNA into the wild gene pool and the range of environments likely to be exposed to the GM fish and hybridised species is not just determined by the organism and its characteristics, but also by the environment itself through ecological factors (cf. lines 1917-1919). The relationship is mutual rather than unilateral which should be considered here.
112	Federal Agency for Nature Conservation	DEU	Step 2: Hazard characterisation	1960: Specification is required about the kind of information requested to assess the characteristics listed in the following sections a) to d). In some cases specifications are indicated (study in line 1964, aquarium experiments and trials in line 1966-1967), while in others, it is open whether assessment involves data collection or not (lines 1963, 1972-1976, 1980, 1990).
113	Federal Agency for Nature Conservation	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	1862 ff.: Persistence and invasiveness of GM fish are covered in 4.1.1 called Gene transfer and consequences (cf. also Figure 5). Although this chapter covers changes in persistence and invasiveness not only of wild relatives - after a successful gene transfer - but of the GM fish itself (1865-1867), we recommend renaming chapter 4.1.1 so that the structuring of 4.1 is in line with the ones of chapters 4.2. and 4.3. We suggest that the chapter title of 4.2.1 “Persistence and invasiveness, including vertical gene transfer” is used in all cases. 1874-1880: The two types of potential consequences of gene transfer described here are incomplete: a ‘Trojan’ gene (lines 1947-1959), which increases and decreases different fitness components at the same time, is another possible consequence. Suggest adding this type to the list and account for it in the following approach. 1899-1900: Specification is urgently required about the kind, quality and quantity of required basic information enabling to characterise the GM fish and identifying biological differences between it and the conventional counterpart. 1906 ff.: We do not agree with the suggested narrowing approach that information to establish if recombinant DNA will change the biology of the GM fish or of hybrids, backcrossed and interspecific hybrids in receiving environments is required only, when the extent and nature of environmental exposure is determined. Information about effects of recombinant DNA on the biology of the GM fish etc. belongs to background information also contributing to the identification of unintended effects (cf. comment on 593 ff.). If lines 1906 ff. have been misunderstood, we recommend clarifying the meaning and requirements for data and information related to the word establish in line 1907. Also, guidance is missing about the kind of information required. 1932-1933: Guidance is required how applicants should justify and/or demonstrate that data from outside the EU are relevant for the range of receiving environments in the EU, bearing in mind that fish behaviour, performance and fitness is itself also influenced by a range of ecological factors, as outlines in lines 1917-1918. This may also apply to lines 4510-4511.
114	Federal Agency for Nature Conservation	DEU	4.1 Specific areas of risk for the ERA of GM fish	Chapter 4.1. considers accidental release of GM fish into the environment, but does not cover release into the environment due to criminal activity as worst-case-scenario. Criminal activities are considered for GM animals and birds (lines 4706-4721) and should be regarded for GM fish as well; especially egg theft. If reared and produced illegally, less strict containment measures and more escaped fish can be assumed. If EFSA is of the opinion that accidental release comprises criminal activities, this should be clarified explicitly here and also in chapter 2. With GM animals and birds, genetic diversity is dealt with in chapter 4.3.2. in terms of breeding and selection. This aspect is missing in chapter 4.1 about GM fish and should be added. We advice referring to the EU Biodiversity Strategy and the conclusions of the European Council which includes aquaculture (cf. 4.3.2.1). It is not sufficient for applicants to evaluate the efficacy and reliability of any mitigating measure. Instead it should be demonstrated that the proposed measures are practical and feasible to reduce exposure and risk, that they work efficiently and reliably under relevant rearing conditions and in relevant receiving environments in order to assess the overall risk. This requirement applies to other subchapters of 4.1. dealing with step 5: risk management strategies as well, namely 2056 ff., 2207 ff., 2343 ff., 2551 ff., 2680 ff. and 2754 ff. (completely missing here) and 2925 ff. 1836-1843: The terminological flexibility is confusing to the reader. We suggest aligning terms and structuring for all three animal groups. For example, the heading of chapter 4.1.3 (impacts on biotic components and processes) lacks a correspondent in chapters 4.2. and 4.3. and more important in Annex II section D.1. of Directive 2001/18/EC which does not use the term biotic components or biotic interactions (cf. lines 2220-2221 in chapter 4.1.3).

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115	Federal Agency for Nature Conservation	DEU	4. Specific areas of risk to be addressed in the ERA	1828-1831: In Figure 5 the issue of pathogens, infections and diseases are considered as interactions with NTO. This is too restricted and should, as listed in Annex II section D.1. of Directive 2001/18/EC, also include impact on population levels of competitors, prey, hosts and symbionts, and predators.
116	Federal Agency for Nature Conservation	DEU	3.7.3 Interplay between ERA conclusions and PMEM	According to chapter 5 and EFSA 2011 effects which are identified but not predictable within ERA like long-term effects have to be addressed initially by CSM.
117	Federal Agency for Nature Conservation	DEU	3.7 Uncertainty analysis	1555: Please add specificity to the list of data limitations that introduce uncertainties.
118	Federal Agency for Nature Conservation	DEU	3.6.2 Guidance to applicants	1502-1505: What does this mean for the PMEM approach? It should be discussed whether the CSM/GS approach suggested by EFSA for GM plants is suitable for GM animals. 1513 ff.: Include a bullet point : experience and data derived from application of biological control.
119	Federal Agency for Nature Conservation	DEU	3.6 Long-term effects	The draft should explicitly mention that assessing long-term effects of animals also involves treatment and disposal of associated by-products. 1427-1430: In terms of cumulative long-term effects chapter 3.6. refers to Directive 2001/18/EC once only and does not mention that effects associated with the interaction of other GMO should be taken into account. Suggest including this aspect and sticking more closely to the recommendation of recital (19) of Directive 2001/18/EC and the wording in Annex II on cumulative effects. 1427-1460: The draft mentions that experiences with invasive species can be informative to get some first ideas about the expected time delay for long-term (environmental) effects of GM animals including factors which determine the delay (propagule pressure) and the speed of spreading. According to the outline of this paragraph, effects deriving from progenies of released individuals are not considered, which however, is very relevant for long-term effects (cf. comment on 475-476). Also, the draft does not refer to biological pest control and what can be learnt from concepts to assess environmental impacts arising from their application. This area should be added here, citing amongst others Bigler et al. (2006) Bigler, F., Babendreier, D., and Kuhlmann, U. 2006. Environmental impact of invertebrates for biological control of arthropods. 2006. CABI Publishing. 1441-1444: Suggest adding invasive species and invasive to the glossary. Please note that invasive is used in different ways in 1441-1444 and 4513-4514. 1445: Suggest citing Henry et al. (2010) in lines 1445 and 1455 as FERA (2010).
120	Federal Agency for Nature Conservation	DEU	3.5.2 Principles of experimental design	1221-1223: The applicant shall not only explain the choice of conditions to rear and manage animals, but also to justify them. In this respect, applying optimum rearing and managing conditions only is not regarded as sufficient. Suggest referring to lines 1243-1263 where the importance is described to expose GM animals to different environmental conditions. 1226-1237: The draft envisages collecting ecologically relevant information about GM animals either through experimental studies under confined conditions or through field data on non-GM surrogates. The draft does not regard experimental studies with the GM animal as mandatory. This does not comply with the step by step principle of Directive 2001/18/EC (recital 24) which determines to gradually reduce the containment of GMOs, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken. Therefore, field data on non GM surrogates should complement, but not replace experiments with the GM animal. Their importance is well described in paragraph 1243-1263. However, the draft does not provide guidance for the deliberate release of GMOs for any other purpose than for placing on the market (cf. scope of the draft and our comment to it) and therefore guidance for Part B is missing. 1304-1322: Figure 4 describes ideal husbandry conditions with an overlapping area of optimum conditions for the variable temperature for the GM

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				animal and the comparator. The draft advises that special care should be taken when interpretation data in case of non-overlapping optima. This is comprehensible, because data from both animals are compared directly to each other. On the other side, it is informative to know how both animals perform and behave over a range of management and production conditions and compare distribution, size and position of their sub-optimum, optimum and non-permissive areas to each other. So applicants should be encouraged to predetermine optimum husbandry conditions for both animals and analyse the results - as described above - also in case of non-overlapping optima. In terms of identifying potential unintended effects this should be done for a range of variables and not be restricted to trait-related once as for temperature in case of the cold-tolerant GM fish. 1392: Suggest adding feed composition and sources of feed ingredients to the list of experimental conditions.
121	Federal Agency for Nature Conservation	DEU	3.4 The use of non-GM surrogates	Cf. remarks to chapter 3.3. Where no comparative assessment is possible a full assessment should be performed. The concept of non-GM surrogates is a very difficult one and may fit only in those cases where food webs, behaviour and ecological functions are really close to those of the GM animals. 1056-1059: Experimental studies performed in confined and controlled conditions are limited by how closely experiments are able to mimic natural conditions. Other than indicated here, this instance is not primarily due to the kind of animal species, but due to principal reasons (consider rewording). Nevertheless, experiments with the GM animal in question are valuable and can provide initial useful information. They can also aid to decide which of several possible non-GM surrogate animals to select (cf. line 1063-1065). Therefore, experiments with non-GM surrogates in nature should not be regarded as replacement for experimental studies with the GM animal, but as further approach to gather data. 1062: Please refer to a certain chapter of the cited book of Kapuscinski et al. (2007a). Please note that while the statement in 1060-1062 refers to animals in general, the cited book is about methodologies for transgenic fish only. 1092-1094: We regard it too optimistic to say that the impacts of introduced species are already well documented. In most cases impacts are only partly known and further and unexpected impacts cannot be excluded even for well investigated species. 1106-1107: The chapter considers the organisms themselves, be they the GM animals or the non-GM surrogates, but ignores associated by-products, wastes, manure etc. and their environmental impacts. It can be reasonably assumed that associated by-products of the GM animal are different from the ones of a non-GM surrogate even if both have similar traits. Therefore, when considering reliability and uncertainty associated with data, model assumptions and non-GM surrogates used, associated by-products should be especially considered and mentioned in the draft. 1138 ff: limits of concern: with animals especially vertebrates the proposed values for the limits of concern seem to be much too high. The possible values should be deduced as proposed in a scientifically sound and transparent manner case to case. The given citation (Heard et al. 2003) is missing. The cited study seems to deal with weed and weed seed banks.
122	Federal Agency for Nature Conservation	DEU	3.3 Choice of comparators	904-915: This paragraph considers the case when no conventional counterpart organism is available and what main components are influencing the potential environmental impacts of the GM animal. According to the mentioned but not followed literal reading of Directive 2001/18/EC the ERA could be restricted exclusively to consider only aspects over and above the introduction of new conventional animals of this species into a receiving environment. While this consideration dismisses that there might be good reasons for not having introduced a conventional species into a certain environment so far, other readings and interpretations of Directive 2001/18/EC with respect to the requirement of a conventional counterpart and the comparative approach are possible as well. One would be that in case of no available conventional counterpart risk assessment and therefore approval is not possible. Another would be that a full risk assessment should be performed if no conventional counterpart is available (cf. our general comments under ABSTRACT and/or SUMMARY). From our point of view the draft should be more reserved with literal readings or otherwise discuss them comprehensively. The outlined suggestion how to interpret a comparative assessment seems to be very forced and strange. 925-932: When justifying the selection of appropriate comparators genetic distance and/or pedigree can aid, but seem to be overemphasised here (cf. also line 866). When using e.g. wild type species or a different species occupying the envisaged ecological niche, it is equally or even more important to compare the biological and ecological characteristics of the selected comparator with the ones of the non-present conventional counterpart. Altogether there are a number of cases where a comparative assessment as developed for plants (and criticised there too for a number of cases) will not be possible and an environmental risk assessment has to be developed that looks into food webs, ecological functions and services as such and the possible harm to these.

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123	Federal Agency for Nature Conservation	DEU	3.3 Choice of comparators	853: In order to achieve easier readability, in concurrence with chapters 3.3.1 and 3.3.2, a specific subchapter on the choice of comparators for GM mammals and birds should be added. 853 ff.: Cf. comment under general comment under ABSTRACT and/or SUMMARY. 865. It is more appropriate to use race instead of species 860-863: The sentence here is presented as an imperative conclusion drawn from the cited passage in Annex II of Directive 2001/18/EC about the use of non-modified organisms. It reads “Hence, where feasible and appropriate, similarities and differences in the interactions between the GM animal and the environment due to the genetic modification and induced changes in management should be estimated in relation to a conventional counterpart.” It implies that, where a conventional counterpart is neither feasible nor appropriate, other approaches are allowed as well. It should be explained in more detail how those assessments where no appropriate comparators exist shall be conducted (cf. also general comments under ABSTRACT and/or SUMMARY). 872-874: It is appreciated that the effect of different genetic backgrounds on the environmental impacts of the event are considered within compositional analysis to account for the fact that in practice commercially available GM animals will often be produced as the offspring from GM animal with other individuals of the same species. At the same time the issue of genetic stability should be considered as well. 878-887: According to this paragraph the ERA should cover the full range of GM animals that might arise from the event being assessed. However, the text is not clear about what coverage actually means here, in which cases data are required, whether data requirements relate to the GM animal only or to associated by-products, wastes etc. (e.g. compositional data from offspring with wild types) as well.
124	Center for Food Safety	USA	Step 6: Overall risk evaluation and conclusions	The overall risk evaluation is missing any consideration of the environmental effects of the changes in fish aquaculture needed for the GM fish. In short, do these fish require more wild caught fish for their feed? The draft guidance fails to properly consider the environmental impact from feeding GM fish in commercial operations. Fish farming already poses a major threat the health and survival of wild fisheries and the expansion of GM fish industries is likely to exacerbate this problem. For example, AquaBounty’s GM salmon is engineered to be fast growing and therefore may require up to five times more food than its non-GM counterpart (See: Abrahams, M.V. and A. Sutterlin (1999). The foraging and antipredator behaviour of growth-enhanced transgenic Atlantic salmon. Anim. Behav. 58: 933-942). Salmon are carnivorous and therefore high up on the food chain so they require large amounts of wild-harvested fish. Total amounts of fishmeal and fish oil needed to feed farmed salmon rose from 261.4 thousand tons to 982 thousand tons between 1992 and 2003, respectively, a number that has no doubt increased since then as the number of farmed salmon have also increased. According to a report from the United Nations’ Food and Agriculture Organization, 50% of the world’s fish oil is used as feed for farmed salmon. Roughly one-third of all small “forage” fish – such as anchovies, sardines, and menhaden – are caught to feed farmed salmon. Farmed salmon typically need to consume three pounds in order to gain a single pound. Seafood species populations are already on the brink of collapse. Any further increased pressure on marine ecosystems – such as GE fish that require up to five times more feed – poses a serious threat to not only the wild populations of fish and seafood but global marine ecosystems as a whole. Not only does feeding smaller fish to larger farmed fish deplete wild populations but their harvesting has also been shown to deplete natural habitats for these fish, further diminishing their numbers.
125	Federal Agency for Nature Conservation	DEU	3.2 Experimental environment	This chapter relates to GM animals only when choosing the right experimental environment, but completely misses associated by-products, wastes etc. Please add this to the text. 801-803: Because of the mobility of animals compared to plants the draft proposes to focus the ERA more on questions related to invasiveness and persistence and thus draws on the considerable scientific literature concerning alien species. However, guidance and specification is missing how to handle the comprehensive literature and how to consider it for the ERA. In addition it seems equally important to assess the food web and ecological functions of the GM animals and possible hybrids with conspecifics and relatives. 824. It seems to be a problematic concept proposing remote islands or lakes as locations where potential harm may not be considered a problem.

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126	Federal Agency for Nature Conservation	DEU	3.1.3 Selection of the relevant receiving environments	739: Please define measurable numbers. 754: For step 2 animal x trait add “associated by-products, waste etc.” to GM animals in the last line of the second bullet point. 762-764: Obviously, this paragraph was introduced to cover for cumulative long-term effects of several consents as covered in recital (19) and Annex II of Directive 2011/18/EC. Please refer to the legal regulation and adopt the key wording mentioned therein. 789-791: It is appreciated that overall ERA should conclude on risk(s) identified in each receiving environment at both national and regional scales.
127	Federal Agency for Nature Conservation	DEU	3.1.2 Identification and characterization of the receiving environments	688: Suggest adding survival to the listing of reproduction, spread and invasiveness.
128	Federal Agency for Nature Conservation	DEU	3.1.2 Identification and characterization of the receiving environments	675-676: According to these lines the receiving environments, the accessible ecosystem and the management system may be one and the same in some highly controlled management systems. Please clarify that this relates to the GM animal and does not necessarily include associated by-products, wastes etc.
129	Federal Agency for Nature Conservation	DEU	3. Cross-cutting considerations	Access to relevant biological test material of the GM animal is important for independent biosafety research to allow for the possibility to test and verify the applicant’s assumptions. This is to make sure that the risk assessment is based on a peer-reviewed and transparent scientific basis. Therefore, the applicant shall be requested to provide access to biological test material well in advance before submitting the application (cf. Reeves et al. 2012). As a minimum applicants shall be required to provide access to biological test material when granting approval. Reeves RG, Denton JA, Santucci F, Bryk J, Reed FA (2012) Scientific Standards and the Regulation of Genetically Modified Insects. PLoS Negl Trop Dis 6(1): e1502. doi:10.1371/journal.pntd.0001502 632: The concept of target and non-target organism developed for GM plants producing insecticidal toxins should be translated into terms relevant for transgenic animals.
130	Federal Agency for Nature Conservation	DEU	2.2 Information to identify potential unintended effects	569-573: The relationship between the extent of the comparative approach and the identification of possible unintended effects is not specified here or elsewhere in chapter 2.2. and missing. In this respect uncertainty analysis shall consider and assess to what extent possible unintended effects could have been identified within the performed comparative approach and when no suitable comparators are available. 580-583: Details and specifications are missing and requested in terms of the kind and status of biological material including by-products, waste etc. to be selected for targeted compositional analysis and in terms of what relevant conditions and environments should be covered when producing the material for compositional analysis. Considerations are missing how environmental safety aspects are best incorporated into compositional analysis and how to deal with knowledge gaps regarding the environment and composition relationship. In this regard the mere adoption of the results of the comparative analysis, including compositional analysis, for the safety evaluation of food and feed from GM animals (line 598 – 604) is insufficient (cf. comment on 593 ff.). 584-588: The text indicates that phenotypic and behavioural characteristics are two different issues. Actually, behaviour belongs to the phenotype or is part of it, respectively. Suggest correcting this passage and others in the draft accordingly, e.g. as follows: “Phenotypic characteristics: unintended effects may also be detected through the comparison of the phenotypic (i.e. morphological, physiological and behavioural characteristics) of the GM animal with the appropriately selected comparator(s) …etc.” Suggest adding conditions at the end of line 588 to account for different rearing conditions. 593 ff.: The placement of GM animals on the EU market for either food/feed uses or non-food/feed uses requires a different set of background information for the assessment. Unfortunately, the following bullet points do not clarify this difference. It is uncertain what background information should be provided for GM animals that are to be deliberately released into the environment except a molecular characterisation (that is also required for food/feed purposes). In order to achieve a better readability, not only the legal reference concerning the data demand should be quoted at this

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				point but it should be briefly summarized what data will be necessary for the assessment. 600: Suggest adding targeted to compositional analysis so the text is in line with 580-583. 601: Add behavioural in brackets so the text is in line with the content in line 584. 614-615: A detailed description is missing what is understood as full set of requirements on molecular characterisation of a GM animal. Line 599 also provides some exemplary general issues only for the alternatively used term comprehensive molecular characterisation.
131	Federal Agency for Nature Conservation	DEU	2.1.5 Step 5: Risk management strategies	517-519: It is not sufficient for applicants to evaluate the efficacy and reliability of any mitigating measure. Instead it should be demonstrated that the proposed measures are practical and feasible to reduce exposure and risk, that they work efficiently and reliably under relevant rearing conditions and in relevant receiving environments in order to assess the overall risk (cf. comment on chapters 4.1., 4.2. and 4.3). 524-530: Please add the following aspect here: The applicant should demonstrate that the management and control measures intended to ensure quality control of the produced GM animals work under full scale production conditions and not just under conditions of a small scale pilot plant.
132	Center for Food Safety	USA	3.3.1 Choice of comparators for ERA of GM fish	The guidance needs to require more complete examination of the feeding habits of the GM fish versus the non-GM comparators. While it is logical to compare GM fish intended for aquaculture with non-GM fish intended for aquaculture it is important to look at the effect of harvesting feed for the GM fish on the wild type fish in the area where the fish are being harvested.
133	Federal Agency for Nature Conservation	DEU	2.1.4 Step 4: Risk characterisation	501-504: The draft recommends considering, where appropriate, representative exposure scenarios including a worst-case-scenario with factors that can lead to high level of exposure. We request complementing the provided examples by criminal activity (e.g. egg theft or kidnapping) as mentioned for GM mammals and birds (cf. 4706-4721).
134	Federal Agency for Nature Conservation	DEU	2.1.3 Step 3: Exposure characterisation	475-476: The draft defines propagule pressure as the combined effect of the number of individuals released into the environment and the number of release events over a specified period of time and regards it a useful element to assess exposure. The matter of progenies and effects deriving there from are excluded here. To our understanding propagules are produced by plants (seeds, spores and others), bacteria and fungi, but not by animals. Since these organisms differ fundamentally in the kind and number of progenies, the concept of propagule pressure should not be applied to animals. The definition and application suggested in the draft disregards effects deriving from progenies which are especially important for long-term effects (cf. comments on 1427-1460).
135	Federal Agency for Nature Conservation	DEU	2.1.2 Step 2: Hazard characterisation	465-467: We advice to use the exact wording of the cited Commission Decision (EC 2002), namely “In some cases, it is not possible ….” instead of “In case it is not possible …”.

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136	Federal Agency for Nature Conservation	DEU	2. Strategies for the ERA of GM animals	287-289: It appears as if the entire wording in line 287-289 is taken from Directive 2001/18/EC except the word common which is added. The recommendation of a common methodology does not exist in Annex II. The text should be corrected or the matter be clarified. 292-297: According to Article 4 paragraph 3 Directive 2001/18/EC the case-by-case principle is a general principle for the environmental risk assessment and not just a question of the required information as indicated here. To avoid misunderstandings, please revise the text here accordingly. 307-311: Add behaviour to the list of areas which indicate alterations in the phenotype and which may allow identifying unintended effects, since behaviour is part of the phenotype. 312-314: Unintended effects are defined in the draft as consistent differences between the GM animal and the appropriately selected comparator(s). This definition could lead to the dismissal of statistically significant differences between test and control as being not consistent (and not relevant) if e.g. they only occur at some of the field trials. While this may be due to chance, the possibility of gene-environment interaction is ignored at the same time. Some differences are only detectable under certain conditions or in certain environments. These differences can still be of high importance. Therefore the word “consistent” should be explained here in more detail. 320-325: Please refer to experience and knowledge with the introduction of invasive species here (dealt with in 1441-1456). In addition it seems to be a non-applicable concept to choose similar or different animals with the same introduced trait as a basis for familiarity. Depending on the biology, ecological range and role the same trait may have very different consequences. Out of our perspective the transfer of concepts developed for crops to animals is not adequate or should be discussed and justified with respect to differences and characteristics of the plant and animal kingdoms. 360-362 Add: [Problem formulation starts with the identification of the aspects of the environment that need to be 360 protected from harm according to environmental protection goals set out by Directive 2001/18/EC and 361 other environmentally-related legislation] "on European and national level" [(see Table 1).] 403-404: Assessment endpoints should also reflect protection goals set out by national legislation of EU member states, e.g. protection goals of national biodiversity strategies. 407-411: Not all assessment endpoints can likewise be translated into quantitatively measurable endpoints. This issue should be addressed and possible consequences in terms of selection of appropriate endpoints be discussed in uncertainty analysis of the ERA which is not yet the case. 451-454: It should be made clear which basic experimental data should be provided in any case to have a sufficient basis for fulfilling this first step of problem formulation. A mere theoretically deduced hazard identification does not seem adequate.
137	Federal Agency for Nature Conservation	DEU	1. Scope of this Guidance Document	The draft is ambiguous and unclear about the kind of releases it covers and about the use of related terms, respectively. The draft does not deal with releases for experimental purposes under Part B of Directive 2001/18/C (247-248), but it avoids saying it covers releases under Part C of the Directive. One might assume this, because the draft “provides guidance to applicants to conduct the ERA of GM animals to be released into the environment and placed on the EU market” (239-241). However, the draft avoids the correct wording of the Directive here, which would be the “deliberate release into the environment”. This is crucial since the term ‘deliberate release’ is defined in Article 2 of the Directive as “any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment”. However, a major part of the draft covers captive GM animals which are held in containment areas (cf. e.g. 4414 and 4442) and therefore they do not fall under Part C, but obviously also not under Part B. The draft deals a lot with risk mitigating measures and the question is whether – according to their purpose – they are actually meant to be containment measures. From our point of view the conclusion from all this is that the guidance for Part B releases which the draft tries to exclude is a hidden but central matter in the draft and needs to be tackled. Cf. also our general comments and comments on 1226-12237 related to the step by step principle. 248-249: The draft does not deal with illegally bred offspring. However, it should address possible specific problems arising there from (cf. comment on 501-504).

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				266: It is not comprehensible why animals producing pharmaceuticals shall be outside of the scope (see comment under general comments under ABSTRACT and/or SUMMARY).
138	Federal Agency for Nature Conservation	DEU	Summary	The entry mask does not provide for the possibility to make some general comments. Therefore we take the liberty to place some general comments under the ABSTRACT and the SUMMARY and/or the beginning of main chapters. ....continuing from comments under the ABSTRACT Further main critical points are: • It is largely unclear in the draft, what background information should be provided for GM animals that are to be deliberately released into the environment except a molecular characterisation. • In several cases a requirement for information is mentioned, but not specified. • It is not sufficient for applicants to evaluate the efficacy and reliability of any mitigating measure. Instead it should be demonstrated that the proposed measures are practical and feasible to reduce exposure and risk, that they work efficiently and reliably under relevant rearing conditions and in relevant receiving environments in order to assess the overall risk (cf. comment on chapters 4.1., 4.2. and 4.3). • Clarification is required throughout the draft document that exposition relates not only to the GM animal itself, but includes associated by-products, waste etc. • The obligation to provide information according to Annex III shall not just apply to impacts on human health of GM fish and GM insects, but to all kind of impacts and all groups of GM animals. • The issue of transboundary movements is missing in the draft and should be added. • Criminal activities should be considered in exposure characterisation and risk characterisation for all kind of impacts and all groups of GM animals and not just for GM mammals and birds (cf. comment on 501-504). The draft document contains valuable considerations in a number of its chapters, but it is not consistently written, lacks guidance in many respects and contains several shortcomings. Because of this and the several critical points highlighted above, we regard the present document as a first draft and would appreciate a second round of public consultation after revision.

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139	Federal Agency for Nature Conservation	DEU	Abstract	The entry mask does not provide for the possibility to make some general comments. Therefore we take the liberty to place some general comments under the ABSTRACT and the SUMMARY and/or the beginning of main chapters. GENERAL COMMENTS We appreciate the document as a first draft guidance on the environmental risk assessment of GM animals and as a completion of the guidance on risk assessment of food and feed from GM animals and on animal health and welfare aspects (EFSA 2012). However we have a number of general and specific further comments. There is a different use of terms regarding the step by step principle as given by Directive 2001/18/EC and in this document. (cf. recitals (24) and (25) of the Directive). Regarding the step by step principle as understood in the Directive a reinforcement of the necessity of a stepwise procedure regarding different scales of releases (and their accompanying data) would be appreciated. Regarding the consecutive approach of the risk assessment procedure as described in this draft guidance document wording and concepts should be clearly separated from the step by step principle as addressed in the Directive (also cf. comments on 517-519 and 1226-1237). The approach of a structured process for the different environmental considerations starting with problem formulation is welcome, but some aspects are missing like inclusive stakeholder participation. The draft interprets the general principle recommending a comparative approach (2001/18, ANNEX II Part B) in a very narrow (and to our understanding) not adequate way. In a number of cases the comparative approach as outlined is not feasible for the ERA of GM animals because “the non-modified organism from which it is derived and its use under corresponding situations” is not available and thus a comparative assessment not possible. In such situations a scientifically sound RA would be a full RA and should be recommended. It is not clear and comprehensible why animals producing pharmaceuticals are outside of the scope of the draft guidance. It should be explained why these applications are not covered in this guidance, especially since transgenic animals producing pharmaceuticals already exist or are being developed (FERA, 2010). Health and animal welfare impacts should not only be included in the section on mammals and birds but also in the section about fish and insects. Especially for the insect section these aspects are of utmost importance given the approaches of altered disease transmission characteristics or toxin production. Hazard identification should be done taking into account not only EU defined protection goals but also national legal obligations.
140	Center for Food Safety	USA	3.3 Choice of comparators	The Guidance Document on line 907 correctly assumes that introducing a species into a receiving environment in which it does not now reside makes it an "alien species". This needs special attention when the species is being raised in one country for live export to another country. This document fails to provide guidance on the requirement to conduct an ERA for GM animals and insects intended for export and open release outside the EU, and EU law mandates that ERAs for GMOs must meet EU standards when intended for export. Regulation (EC) No 1946/2003 of the European Parliament and of the Council on Transboundary Movements of Genetically Modified Organisms from 2003 incorporates the Cartagena Protocol on Biosafety to the Convention on Biological Diversity into European law. According to Regulation (EC) No 1946/2003, “exports of genetically modified organisms intended for deliberate release into the environment should be notified to the Party or non-Party of import, allowing it to make an informed decision, based on a risk assessment carried out in a scientifically sound manner.” This risk assessment must be consistent with Annex II to Directive 2001/18/EC which outlines the standards and methodology to be followed for any Environmental Risk Assessment in the European Union or for any GM product intended for export. In other words, any export of a GM animal or insect must go through an ERA that meets EU standards before they are exported to a country outside the EU.

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141	Soil Association	GBR	3.8 Aspects of GM animal health and welfare	3.8 Aspects of GM animal health and welfare Line 1752: The first production stage for GM animals involves establishing the transgenic trait. The process of obtaining eggs is invasive if taken from live mammals, and implanted genetically modified eggs lead to many stillbirths, miscarriages or invasive surgery on the mother (GeneWatch UK, 2002). Ethical issues are similar to those associated with cloning mammals (EGE, 2008) but have been entirely neglected here. Loss of genetic diversity (due to the production of genetically identical herds of cows or farmed chickens or fish) also needs to be considered as it may increase vulnerability of he animals to infection. 3.8.1 Health and welfare aspects for GM mammals and birds Line 1797: Loss of genetic diversity needs to be considered as mass production of identical GM mammals or birds may increase vulnerability to infection.
142	Soil Association	GBR	Background as provided by the European Commission and EFSA	Line 187: Whilst it is correct to state that ethical and socio-economic issues are outside EFSA's remit, the issuing of draft Guidance before such issues are addressed is premature. The production of GM mammals, including pets and farm animals, raises many important ethical issues (GeneWatch UK, 2002) and much of the harm to animal welfare (e.g. aborted foetuses) is caused at the production stage of GM mammals. For example, in the case of production of transgenic pigs with increased levels of omega-3 fats in their meat, a total of 1,633 reconstructed embryos were transferred into 144 pigs; 12 early pregnancies were established, and five of them went to term leading to 12 (ten alive and two dead) male piglets being born by either caesarean section or natural delivery (Lai et al.,2006). Ethical concerns about this process have been completely ignored. In the case of GM fish, the North Atlantic Salmon Conservation Organisation (NASCO) states in the Williamsburg Declaration: "In view of the current lack of scientific knowledge on the impact of transgenic salmonids on wild salmon stocks, the use of transgenic salmonids should be considered a high-risk activity. There should be a strong presumption against any such use" (NASCO, 2006). There is strong opposition to the introduction of GM fish from fishing organisations and producers in the EU. Yet EFSA's starting point seems to be that the production and deliberate release of GM animals is ethical and acceptable. Oxitec (which is acting as an advisor to the Working Group on Insects) has already been strongly criticised for failing to seek informed consent for its releases of GM mosquitoes overseas (Enserink, 2010) and it is widely recognised that informed consent is needed for releases of genetically modified disease vector species (Macer, 2003; Macer, 2005). Yet the Guidance does not even mention informed consent as an issue that must be addressed. Food safety, consumer acceptability and trade issues associated with the use of GM agricultural pests have also been ignored (see comments on lines 267-272) as have the implications for plant pest control regulations.
143	Soil Association	GBR	Summary	Line 48: It is unclear to the reader why other animals, e.g. amphibians, molluscs, crustacea, are omitted, despite their inclusion in patent applications (AquaBounty , 2011). The draft Guidance should be clear about whether it is attempting to cover all GM animals or not. Line 57: The summary refers to selection of receiving environments but there is virtually no content in the consultation relating to this or any description of how this might be controlled. For example, the UK company Oxitec is working on genetically modified (GM) Aedes albopictus mosquitoes (Labbé et al. 2012) which are an invasive species currently being monitored due to concerns they will spread tropical diseases in the EU (ECDC, 2009). There is no discussion of whether releases of GM Aedes albopictus would be allowed in parts of the EU but not others and if so, whether they could possibly be restricted to particular receiving environments. There are concerns about how in practice this could be achieved (Angulo & Gilna, 2008a &b).
144	Soil Association	GBR	Abstract	Line 17: It is unclear why other animals e.g. amphibians, molluscs, crustacea are omitted: this means the Guidance is far from comprehensive, even for GM animals envisaged in current patent applications (e.g. AquaBounty, 2011). Due to the extensive errors, omissions and inconsistencies noted in this response (including a need to identify mechanisms through which the many issues which fall outside EFSA's remit can be addressed), there will be a need for re-consultation once revisions have been made. The vast extent of the animal kingdom means that revised guidance should not attempt to encapsulate more than one genus at a time. The scale of the task required to provide meaningful guidance on even a small proportion of possible applications is enormous. For example, there is a current project to sequence the genomes of 5,000 insect and related arthropod species over the next 5 years (i5k: http://arthropodgenomes.org/wiki/i5K). This will create the potential for all these species to be genetically modified in a wide variety of ways.

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145	Environment Canada	CAN	Step 5: Risk management strategies	As indicated in the Guidance Document, risk management measures and strategies need to address potential hazards and be conservative in nature by considering high exposure scenarios as appropriate and where exposure is possible. However, even though strategies might be proposed for preventing the release of a companion animal into the wild (lines 5994-5996), it is unclear how efficacy of these strategies will be demonstrated, and how this will be linked to a risk reduction in the overall assessment.
146	Environment Canada	CAN	Step 2: Hazard characterisation	The Guidance Document presents a comprehensive and community based approach to identify the potential impact a GM organism may have on its receiving environment. However, in table 7, it is unclear why the one-way indirect interactions with the GM animal for predator 2 would be negative via the top predator. With an additional food source, one would expect that the predation pressure of the top predator on predator 2 would be reduced, giving a net positive effect on predator 2.
147	Environment Canada	CAN	Step 1: Problem formulation (including identification of hazard and exposure pathways)	The Guidance Document provides a good explanation for the need to understand the interaction between the GM animal and target organisms. However, it is unclear in lines 5430-5432, how any identified mechanism will be considered in the risk assessment. Is this consideration examined in relation to the same potential that exists for other non-GM alternatives? That is, if the applicant can demonstrate that the same potential exists with alternative pest control options, and that the development of resistance is no more likely with this technology than any other, can further analysis be omitted? Also of note is that the information described to address this section seems far more involved than what was requested under the GM insect portion of the document, which simply requests applicants to describe how resistance to the GM insect applications, or any other reduction in efficacy, could occur (line 3398). It is unclear why mammals and birds would require a far more intense examination of this potential as compared to insects particularly when the establishment of insects in novel environments can generally be more difficult to control.
148	Environment Canada	CAN	Step 2: Hazard characterisation	The Guidance Document provides a good explanation for the need to understand the interaction between the GM animal and target organisms. However, it is unclear in lines 5430-5432, how any identified mechanism will be considered in the risk assessment. Is this consideration examined in relation to the same potential that exists for other non-GM alternatives? That is, if the applicant can demonstrate that the same potential exists with alternative pest control options, and that the development of resistance is no more likely with this technology than any other, can further analysis be omitted? Also of note is that the information described to address this section seems far more involved than what was requested under the GM insect portion of the document, which simply requests applicants to describe how resistance to the GM insect applications, or any other reduction in efficacy, could occur (line 3398). It is unclear why mammals and birds would require a far more intense examination of this potential as compared to insects particularly when the establishment of insects in novel environments can generally be more difficult to control.
149	Environment Canada	CAN	Step 2: Hazard characterisation	The Guidance Document provides excellent examples that clearly help the reader understand many of the technical and scientific considerations presented and how these considerations are being used in the overall risk assessment. However in the example provided in lines 5256-5258, it is not obvious why a hypoallergenic companion animal would have a change in pathogen transmission or even contact rate with other animals when compared to a non-hypoallergenic one.
150	Environment Canada	CAN	4.3.2 Vertical and horizontal gene transfer	Section 4.3.2 clearly recognizes that genetic diversity is important to maintaining healthy populations and the impact of introduced genes in wild populations through vertical or horizontal gene transfer may have negative impacts. However, given this impotence, it is unclear why the same level of emphasis with respect to genetic diversity that was put forth for mammals was not considered for insects, and was only briefly discussed for fish.
151	Environment Canada	CAN	Step 3: Exposure characterisation	The risk of sabotage or other anthropogenic involvement in the unauthorized and intentional release of a confined GM organism into the environment is important to consider when implementing risk management measures. Often times, the measures in place are based on a qualitative analysis. However, in lines 4717-4721: It is unclear how an applicant would estimate the risk of sabotage, kidnapping, or theft and its likelihood, uncertainty and what estimates one would choose/justify for numbers released in such an event. It is also unclear why this would be an important consideration for mammals/birds but not mentioned under other sections dealing with fish or insects.
152	Environment Canada	CAN	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Section 4.2.5, “environmental impact of the specific techniques used for the management of GM insects”, seems to focus heavily on the management of any effects the organism had on non-target organisms (i.e. increase pesticide use for a non-target pest now filling the niche once occupied by the pest the GM organism successfully controlled), as opposed to production practices for the organism. This appears somewhat inconsistent with what was addressed in its equivalent sections for fish and for mammals. It would be useful to explain this discrepancy.

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153	Environment Canada	CAN	Step 2: Hazard characterisation	Lines 3937-3938: The meaning of this sentence is unclear.
154	Environment Canada	CAN	Step 3: Exposure characterisation	It is well known that releases from sea cages do occur in the aquaculture industry and several studies have attempted to quantify these releases and their impacts on the receiving environment. The guidance document accurately expresses the importance of considering these potential releases where appropriate. Lines 2531-2532: It is unclear how an applicant would estimate the likelihood and frequency of escape for captive GM fish. Is this estimate based only on normal operating procedures, in which case should this number not be close to zero, or does it include releases due to catastrophic events? If the estimate includes releases from catastrophic events, can guidance be provided as to how these estimations should be made in a systematic way?
155	Environment Canada	CAN	3.6.1 Categories of long-term effects	The ability to predict biotic and abiotic changes that may influence survival and proliferation of an introduced organism in an environment remains a challenge particularly given the dynamics of climate change. This challenge further complicates the science of risk assessment when it comes to GM-animals. Lines 1475-1483: It is unclear how an applicant would be able to incorporate changes on an evolutionary or climate change timescale in their risk assessment, including “ecological surprises”. It is also unclear how an applicant would be able to predict and incorporate future changes in management practice of an industry into their assessment. If management practices play a key role in reducing risk, it would be prudent to require that management practices continue to achieve specific risk management objectives over time, even when industry practices change and particularly in response to climate change.
156	Environment Canada	CAN	4.1.1 Gene transfer and consequences	It is clear within the Guidance Document that both direct releases into the environment (non-captive and semi-captive) as well as confined (captive) uses are covered. It is unclear however the extent to which the applicant must address the specific areas of risk (hazards) when the organism is considered captive. In all scenarios, risk management strategies are considered after a thorough examination of hazards. However, if the organism is captive, with no intended release to the environment, and risk management measures are considered to be appropriate and as fail-safe as possible, to what extent must hazard levels be addressed? To what extent are uncertainties acceptable if appropriate confinement is in place? This is perhaps best demonstrated in Figure 6 in relation to GM fish, however it is not entirely clear here or throughout the rest of the document In Figure 6, it is unclear whether or not an applicant of an organism that is considered captive with little to no accidental release potential, but could survive if released into the right environment, would be able to answer “no” to the question “Will GM fish be released or escape and survive outside rearing system?”. It is also unclear whether or not an applicant of an organism that is considered captive could answer “no” to the question “Will GM fish reproduce? “ when founder animals and breeding stock are expected to be reproductively competent while the majority of commercial organisms may be produced to be infertile. To summarize, it is unclear to what degree data requirements will be reduced as a result of “containment/captivity”, or how incidents such as theft or catastrophic failure should increase the requirement to generate data and to address uncertainties when identifying and characterizing potential hazards.
157	Environment Canada	CAN	Step 1: Problem formulation (including identification of hazard and exposure pathways)	It is clear within the Guidance Document that both direct releases into the environment (non-captive and semi-captive) as well as confined (captive) uses are covered. It is unclear however the extent to which the applicant must address the specific areas of risk (hazards) when the organism is considered captive. In all scenarios, risk management strategies are considered after a thorough examination of hazards. However, if the organism is captive, with no intended release to the environment, and risk management measures are considered to be appropriate and as fail-safe as possible, to what extent must hazard levels be addressed? To what extent are uncertainties acceptable if appropriate confinement is in place? This is perhaps best demonstrated in Figure 6 in relation to GM fish, however it is not entirely clear here or throughout the rest of the document In Figure 6, it is unclear whether or not an applicant of an organism that is considered captive with little to no accidental release potential, but could survive if released into the right environment, would be able to answer “no” to the question “Will GM fish be released or escape and survive outside rearing system?”. It is also unclear whether or not an applicant of an organism that is considered captive could answer “no” to the question “Will GM fish reproduce? “ when founder animals and breeding stock are expected to be reproductively competent while the majority of commercial organisms may be produced to be infertile. To summarize, it is unclear to what degree data requirements will be reduced as a result of “containment/captivity”, or how incidents such as theft or

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				catastrophic failure should increase the requirement to generate data and to address uncertainties when identifying and characterizing potential hazards.
158	Environment Canada	CAN	3.4 The use of non-GM surrogates	Section 3.4 discusses the use of non-GM surrogates to replace the GM animal so that experiments can be conducted in nature. One of the options discussed for a non-GM surrogate is selectively bred and domesticated strains that express phenotypes similar to the GM animal. The traits of such a selectively bred animal would be heritable, and the very fact that such an animal can act as a surrogate (i.e. they are expected to have similar effects in the wild as a GM animal would) raises two questions: 1) If it is the trait itself and not the fact that the organism is GM that results in the potential hazard then why is it that only the GM animal is being regulated? and 2) if the non-GM animal is expected to behave the same as the GM animal (i.e. as an appropriate surrogate) should one not be concerned about the potential hazards posed to the environment by the release of the non-GM surrogate in field studies?
159	Environment Canada	CAN	1. Scope of this Guidance Document	Section 1 clearly outlines the scope of what the Guidance Document (GD) covers with respect to the type of organism and the commercial and any associated unintended or accidental release of GM animals into the environment. Releases for experimental purposes appear to be intentionally excluded. Yet, section 3.2 discusses the experimental environment and provides guidance on using suitable containment measures. It is unclear in the GD whether approval is or should be required prior to the initiation of a field study, and if there is, what would be required for an approval.
160	Environment Canada	CAN	Assessment	General comment: The Biotechnology Section of the Emerging Priorities Division at Environment Canada is pleased to provide comments and feedback through his public consultation on the draft Guidance Document on the Environmental Risk Assessment of Genetically Modified Animals developed by EFSA. This Guidance Document (GD) provides a good overview of the myriad of considerations that could be examined and studied during the risk assessment of a Genetically Modified (GM) animal prior to its release into the environment. As highlighted throughout the GD, a thorough examination of true or potential hazards of the GM animal to the environment and human health is essential in a scientifically sound and defensible risk assessment. The GD also clearly and accurately recognizes that in many cases, uncertainties and ambiguities will remain due to the novelty of the technology, lack of direct evidence on the GM animal or on the parental strain. The uncertainties may at times be addressed through information available on appropriate surrogates, but often times, Risk Management (RM) measures may be necessary to ensure environmental and human health safety. Physical or biological containment may play important roles in the RM measures used in the mitigation of potential risks. However, in the GD, the degree to which containment may offset the need to extensively study potential hazards is unclear (particularly when failure of containment is possible for example due to human error, catastrophe or sabotage). Also unclear is the need for some of the potential hazard considerations to be examined given the actual traits expressed by the GM animal (i.e. actual physiological or behavioral differences between the GM animal and its non-GM comparator). Finally, it is unclear to what degree some of this information requested will actually affect the risk assessment outcome, as such, how much effort must be put into quantification of the hazard, likelihood and uncertainty when the impact to the risk assessment outcome may be minimal.
161	SELF EMPLOYED	GBR	3.5.1 General Principles	I would urge you to take a look at lines 165 to 168. The EFSA is not competent to assess environmental risks as it has no remit or expertise in this area.
162	Advisory Committee on Releases to the Environment (ACRE)	GBR	5. Post-Market Environmental Monitoring plan	ACRE welcomes the clear and concise presentation of this section of the guidance, which covers the key issues. This contains a suitable level of detail to support the construction of a post market environmental monitoring plan. ACRE considers that lines 6444-6451 should be amended to make it clearer that CSM is not required in all cases. It should not be assumed that long term or large scale effects will occur because of the genetic modification. CSM for long term or large scale effects should be designed based on a clear hypothesis. Monitoring for efficacy of risk management measures (lines 6452-6464) should only be required if efficacy has not been demonstrated in the ERA. In all cases implementation of risk management measures should be monitored. At line 6492 it is stated that the objective of GS is to determine causality. This is unlikely to be possible using GS approaches. The objective should be to determine whether a correlation exists between adverse effects and the presence of a GM animal. The text should be amended to reflect this.
163	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.3.8 Impact on non-GM animal health and welfare	Only the chapter on GM mammals and birds treats this as a separate topic. Specifically it considers the issue of whether the GM animal (particularly companion animals) presents a new hazard for the health and welfare of other animals. The majority of issues have, however, been covered in section 4.3.3 and it is questionable whether this separate section is needed.

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164	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.3.9 Impact on human health	see comments at 4.1.7
165	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.2.6 Impact on Human Health	See comments at 4.1.7
166	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.1.7 Impact on human health	As with other sections, improvements could be made to ensure consistency across chapters. ACRE also notes that this section of guidance in particular gives the impression of being fully comprehensive in considering all possible risks, but does not (and cannot for a case by case assessment) manage to achieve this. For example the impact on human health section (pg 68-71) lists examples of pathogens, transmitted by fish, which cause disease in humans. Such an overview is useful, but not appropriate for a guidance document as it raises the possibility that applicants will focus on the identified risks and neglect to consider others which would be more relevant.
167	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.3.7 Environmental impact of the specific techniques used for the management of GM mammals and birds production systems	See comments at 4.1.6
168	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	See comments at 4.1.6
169	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.1.6 Environmental impacts of the specific techniques used for the management of GM fish	In general this section of the guidance deals with similar themes across all three chapters. It benefits from relatively simple presentation. ACRE notes, however, that there are differences which are not justified by the type of animal under consideration. Resolving this would increase clarity as to the approach and information required. ACRE considers that the information requirements should be clearly based on problem formulation. If the type of modification does not indicate that a change in management practice is required, it should be clear that information on the range of management and production systems (e.g. lines 2723-2726 and 6152-6154) is not needed in the application. ACRE considers that the environmental impacts of any production system which will be located in an area where it does not presently exist, or increased in scale, should be assessed in the same way, using risk-benefit analysis, whether or not this involves the use of GM animals (lines 2714-2722 and 4070-4073). The language used in lines 4070-4075 could be improved to make it clear that this applies to production systems where GM insects are used commercially, rather than units where GM insects (e.g. sterile insects) are produced under contained conditions.
170	Advisory Committee on Releases to the Environment	GBR	4.3.6 Abiotic interactions	See comments at 4.1.5

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	(ACRE)			
171	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.1.5 Abiotic interactions	The chapters on GM fish and mammals/birds replace the topic 'biogeochemical processes' with the heading 'abiotic interactions'. The chapter on GM insects does not include this as a separate heading. The GM fish chapter defines two relevant aspects of abiotic interactions: 1) altered tolerance of the GM fish to abiotic factors and 2) alterations in the way the GM fish affects its abiotic environment. The chapter on mammals and birds considers only the second of these two points under this heading. This chapter provides a more holistic description of the effects on ecosystem processes than the corresponding chapter on GM fish. There is no clear reason why this should be handled differently due to the type of animal being considered. ACRE notes that background variability can make small impacts on abiotic processes difficult to quantify experimentally. It is therefore important that the ERA is based firmly on problem formulation informed by the characteristics of the GMO. It is also important that changes due to the introduction of a GM animal are be placed in the context of the magnitude of change caused by other vectors.
172	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.3.5 Interactions of the GM mammals and birds with non-target organisms	See also comments at 4.1.3 The subsection on GM mammals and birds is long and unnecessarily complex. In its current form it would be difficult to use as practical guidance in constructing an ERA. ACRE is concerned that the opening statement in the problem formulation section, which refers to 'environmental concerns' (lines 5506-5509) moves away from a structured tiered approach where the first step is the consideration of the genetic modification and the genetically modified organism. One reason for the complex structure of the guidance is the inclusion of 'scenario 2' where the GM animal may be released, or escape, to ecosystems where there is no conventional counterpart. ACRE notes that this is not an issue which is unique to GM mammals and birds and refers to its earlier comments on Section 3.3. The primary concern will be the presence of an entirely alien species, of which the genetic modification will be only a small component. Of relevance to this, the guidance uses the example of a GM domestic cat throughout (e.g. lines 5570-5578), without reference to the substantial existing impact of its conventional counterpart. With reference to lines 5579-5597, ACRE questions the need for the detailed explanations accompanying the three categories of containment; captive, semi-captive and non-captive. The reference to NTOs in the owners' houses is also questionable when considering how this could relate to assessment endpoints and protection goals. ACRE notes that sections of the guidance are adapted from EFSA's guidance on GM plants, but does not consider that Table 6 (pg 6), which simply lists a range of taxonomic groups, is a necessary or useful addition. A modified decision tree has been included in Figure 7 (pg 135), but the accompanying text has been changed in a way which does not clearly lead the reader through the process. The meaning of the sentence beginning at line 5654 and the circumstances where the four step process should be applied are not clear. The sentence at line 5677 appears to imply that the four step process is only relevant for scenario 2, which is not the case. In addition ACRE notes that the third step has been expanded to require the construction of a food web (lines 5703-5717). The reasons for making this a de facto requirement are unclear. The accompanying description of applying to constructing a food web in the hazard characterisation section (lines 5762-5809) is overly prescriptive. The description provided under the heading 'focal species for in-depth investigation' (lines 5812-5946) is complex. The decision tree in Figure 9 appears to imply that in all cases experiments will need to be performed to quantify effects. ACRE does not consider that this should be the case. This will lead to the provision of data on variables which are not relevant for the ERA of the GMO, where the baseline is not understood and where the biological/ ecological significance of differences are unknown.
173	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.2.4 Interactions of the GM insect with non-target organisms	See also comments at 4.1.3 The subsection on GM insects is more complex than the corresponding section on GM fish. The focus on the genetic modification and the characterisation of the GMO being central to the problem formulation is not sufficiently prominent in the text. This should be identified as a key issue at the beginning of each section. Greater emphasis should also be placed on the tiered approach to testing. Lines 3704-3738 refer to effects on abundance or species composition of natural enemies and the pest regulation service they provide. ACRE considers that this section should include reference to appropriate comparators i.e. the impacts of alternative methods of control on these NTOs.

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174	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.1.3 Impacts on biotic components and processes	There are major differences between the subsections on non-target organisms in the guidance. In the chapter on fish, the title is altered to impacts on biotic components and processes and consideration of biogeochemical processes is included in this section. The corresponding sections of the insects and mammals/birds chapters retain the non-target organisms title. There is little consistency in the structure of this subsection across the three chapters beyond the use of headings from the six stages of the risk assessment. Although the guidance relates to different types of animals, there should be common core themes which are not influenced by this. In particular this should be the case for the chapters on GM fish and mammals/birds. Common themes are not, however, clearly identified in the current structure of the guidance. For example, direct and indirect effects will need to be considered for all types of animals and in all cases it will be more challenging to characterise indirect effects. For all animals there are various different possible interactions such as predator-prey, symbiotic and competitive interactions. This could be dealt with preferably by pulling this together in a common introduction or by repeating the same text in different subsections. ACRE considers that the simpler framework provided in the guidance on GM fish is more suitable for a guidance document for case specific risk assessment. For all three chapters, ACRE considers that the guidance should make more explicit reference in the problem formulation section to the type of genetic modification and characterisation of the genetically modified organism (i.e. intended and unintended effects). The use of decision trees would help to support the text in the GM fish and insects chapters. The emphasis should be firmly placed on problem formulation and identifying NTOs which may be affected by the genetic modification. The subsection on GM fish contains a suitable level of detail. In places improvements could be made and the tiered approach should be more evident. The hazard characterisation section (pg 57) identifies potential differences, but the link to problem formulation and hazard is less clear. ACRE notes that this subsection refers to ecosystem effects and the impacts on focal species. Although equally valid, this differs from the language used in the other chapters, which refer to ecosystem services, protection goals and assessment endpoints.
175	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.3.4 Interactions of the GM mammals and birds with target organisms	See comments at 4.1.4
176	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.3.3 Pathogens, infections and diseases	See comments at 4.1.4
177	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.2.3 Interactions of the GM insects with target organisms	See comments at 4.1.4
178	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.1.4 Pathogens, infections and diseases	Another example where consistency could be improved is the handling of the topic of target organisms. The chapter on GM fish replaces this topic with a subsection titled ‘pathogens, infections and diseases’. The chapter on GM insects retains the title interactions with target organisms and specifically considers sterile insects, which is a valid interpretation. The chapter on mammals and birds contains subsections on both target organisms and pathogens, infections and disease. Again, the reasons for the differences between the guidance on fish and mammals/birds is unclear. A strength of this subsection in the GM fish chapter is that the problem formulation section begins by identifying a ‘key question’ (lines 2466-2468). This is followed by a description of next steps if the answer to the question is yes. This helps to clearly delimit information requirements. As an alternative to using decision trees ACRE considers that the guidance could be improved if each subsection of the guidance identified a key question with equal clarity and at the same position in the text.
179	Advisory Committee on	GBR	4.3.2 Vertical and horizontal gene	See comments at 4.1.2

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	Releases to the Environment (ACRE)		transfer	
180	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.2.2 Horizontal gene transfer	See comments at 4.1.2
181	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.1.2 Horizontal gene transfer	In places the horizontal gene transfer (HGT) subsection uses similar language across all three chapters, but there are also differences which do not always seem to be justified by differences in the types of animal considered. It would be more useful to clearly identify specific issues relating to HGT for each of the three animal types which could require consideration in the risk assessment, rather than leaving this for the reader to determine. In general ACRE recommends that sections on HGT begin with the consideration of whether in a worst case scenario, in which HGT did occur, the effects would be harmful. As mentioned previously, for mammals and birds, vertical gene transfer is also considered in this section (lines 4785-4884). It is explained that in this section, vertical gene transfer is considered in the context of possible effects on loss of genetic diversity. It is not, however, clear why this topic should be handled differently in the fish and mammals/birds chapters. ACRE considers that here the guidance goes beyond the scope of specifically considering the effects of the genetic modification and into a wider consideration of the effects of selective breeding (lines 4811-4830).
182	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.3.1 Persistence and invasiveness of GM mammals and birds and vertical gene transfer to wild and feral relatives	See comments at 4.1.1
183	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.2.1 Persistence and invasiveness, including vertical gene transfer	See comments at 4.1.1
184	Advisory Committee on Releases to the Environment (ACRE)	GBR	4.1.1 Gene transfer and consequences	Three different headings are used across the three chapters for the first ‘area of risk.’ In two cases, vertical gene transfer is also considered only under this heading. For mammals and birds, vertical gene transfer is also considered under a separate heading; ‘vertical and horizontal gene transfer’. ACRE welcomes the inclusion of a decision tree in this subsection on GM fishes (pg 49). The chapter on mammals and birds uses an alternative approach of posing a series of questions accompanied by detailed text. ACRE considers that the same approach should be taken in each section of the guidance and that the use of decision trees is preferable in that it clearly and concisely illustrates the tiered approach to risk assessment. In general the text in the section on GM mammals and birds is overly complex and has a tendency to lose sight of problem formulation in discussing the types of information which may be needed. In the guidance on GM fish two categories of potential consequences of gene transfer are identified (lines 1874-1880). It is also noted that the transfer of DNA into wild species is not an environmental risk in itself (1867-1871). ACRE considers the approach of clearly setting this out in the problem formulation subsection to be helpful.

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185	Advisory Committee on Releases to the Environment (ACRE)	GBR	4. Specific areas of risk to be addressed in the ERA	The guidance needs significant revision to improve consistency between chapters, remove repetition within chapters and to clearly formulate the scope of each subsection. Clear efforts have been made in parts of the text to adopt the same approach across all chapters, whereas in other areas, differences in the scope or detail of the text are not justified by differences in the type of animal being considered. In general, these chapters provide an informative synthesis of criteria and recommendations for assessing the three different types of GM animals. ACRE notes that the level of detail, the length, and in places the scope, of the chapter on GM mammals and birds far exceeds that of the other chapters. This chapter in particular would benefit from revision to simplify the text and ensure it is aligned with the other two chapters. The six step risk assessment The extended six step risk assessment (see comments at 2.1) and its use as a framework for each section ('area of risk') results in a great deal of unnecessary repetition in the text. In places the identification and characterisation steps are not clearly separated. Improvements could be made to many of the subsections on hazards, which are often discursive, providing details of the types of change which could result from genetic modification, but without clearly linking this to identification of a hazard. Exposure characterisation for the main part involves the same considerations across each subsection. In some cases the risk characterisation step does little more than reiterate the need for hazard and exposure to be considered together. In most cases the overall risk evaluation and conclusions section repeats the same text to state that management measures should be taken into account and uncertainties should be identified. For each section it would be useful to refer back to Section 2 and consider whether there are any novel features of the type of animal which require specific consideration and restrict the discussion to these points. If there are no novel features, the reader can be referred to the guidance in section 2. ACRE recommends that the guidance is carefully reviewed to remove repetition and focus on identifying key messages and so generate a document which is easier to engage with. Annex II topics Annex II of Directive 2001/18/EC sets out a series of topics on which information should be included, as appropriate, in the ERA. It is stated that this information should be provided with a view to drawing conclusions on the environmental impact from the release or placing on the market of a GMO. The guidance on the ERA of GM animals defines these topics as 'specific areas of risk.' ACRE has concerns about the use of this term and this prescriptive approach of pre-defining areas of risk. This may lead applicants to restrict their risk assessment and focus on these areas without considering other potential risks. It is apparent that the topics listed in Annex II do not provide a good fit the requirements for an environmental risk assessment for GM animals. The guidance attempts to use the topics from Annex II as a framework by translating these into 'areas of risk' with relevance for GM animals. The authors of the three chapters have taken different approaches to achieve this. As a result, the subsections are not consistent with each other. The content and scope differ in places where this is not justified by the type of animal under consideration. ACRE considers that the lack of consistency results in confusion as to the scope, purpose and information requirements for each subsection. Careful revision will be needed to ensure that the only reason for differences in the text is a fundamental difference in the type of animal being considered.
186	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.8 Aspects of GM animal health and welfare	This section could be streamlined to simply provide reference to the EFSA guidance on animal health and welfare. It would, however, be useful to highlight here that animals modified for disease resistance could act as a reservoir for disease and that this should be considered in the environmental risk assessment. The rationale for including lines 1785-1788 which state that evidence would be needed to support claims of health benefits is not clear in this context and not consistently applied to other areas of the guidance. In addition, lines 1789-1797 appear to extend requirements for GM animals to beyond those required for conventionally bred animals.
187	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.7 Uncertainty analysis	ACRE considers this section is unnecessarily complex, prescriptive and overly academic for inclusion in a guidance document. This section is greatly expanded relative to that provided in EFSA's guidance on the ERA of GM plants. The key focus should be on identifying areas of uncertainty and the potential implications of such uncertainty. In addition key questions are whether uncertainty can be addressed by the provision of further information, through management measures or whether case-specific monitoring should be required. In order to ensure a proportionate approach to uncertainty, it may also be appropriate to take analysis of benefits into account. ACRE recommends that this section be simplified to cover these key points with reference as appropriate to supporting literature.

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188	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.6 Long-term effects	The legislation, and in particular Commission Decision 2002/623/EC, identifies issues that ERAs should take into account when considering the long-term effects of GMOs. ACRE notes, however, that there is no credible a priori reason why the genetic modification of an organism should require specific consideration of long-term effects. ACRE considers it important that the guidance frames the consideration of potential long term effects clearly against the background of problem formulation. Baseline data should only be required as part of the ERA in situations where a risk hypothesis exists as to how long-term effects could occur. ACRE does not agree with the statement that long-term effects are poorly investigated for most animal species (lines 1441-1442). There are many studies on long-term ecological effects and population dynamic databases that could be used to develop base-lines for an ERA.
189	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.5 Experimental design and and statistics	ACRE considers that the guidance is overly complex and it will therefore be challenging for applicants to determine how to use the statistical protocol in experimental design. ACRE notes that for observations collected over multiple time points, requiring time series analysis and using ANOVA typed approaches, careful consideration of repeated measures effects will be required.
190	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.4 The use of non-GM surrogates	This section of the guidance suggests that non-GM surrogate animals could be used to replace the GM animal so that experiments can be carried out in the natural environment (lines 1060-1062). ACRE is concerned that this implies that the risks are reduced simply because a non-GM approach is used, which is not the case. Lines 1066-1070 suggest that non-GM sterile animals could be used in place of GM sterile animals. ACRE acknowledges that in some specific cases, for example for sterile insects, useful information may be derived from examining existing practices using non-GM techniques. Specifically generating and releasing sterile animals as a proxy for studying sterile GM animals would, however, deliver limited information of relevance to the GM trait. Non-GM sterile animals should not automatically be considered to have a lower environmental risk than GM sterile animals. Lines 1071-1074 suggest that strains which express phenotypes similar to those of GM animals may be used as a proxy. The example of fast-growing farmed salmon replacing GM salmon with a similar growth phenotype is provided. There is again no reason to expect that information relating to the genetic transmission of the trait will be equivalent or that the risks of releasing an organism with the same phenotype produced by conventional breeding will be any less than the risks of releasing an organism produced by genetic modification. ACRE agrees with the statement that non-GM surrogates may provide a useful source of historic or parallel data (lines 1084-1086), but sees limited potential for the use of non-GM surrogates in specific experiments to obtain de novo data (lines 1088-1089) apart from in avoiding the regulatory requirements of conducting a research trial using a GMO.

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191	GenØk - Centre for biosafety	NOR	5. Post-Market Environmental Monitoring plan	Monitoring provisions Beyond the relevant questions or protection goals that monitoring would be designed to address, the specific provisions for the development of a monitoring plan for GM animals is critically lacking in the guidance. The recent guidance document on Monitoring of GMOs developed under the Cartagena Protocol contains the basic provisions for both a CSM (case specific monitoring) and GS (general surveillance) along with points to consider foran effective and efficient monitoring plan. These elements should be included in the EFSA guidance as well. This includes, briefly, 1. Choice of indicators and parameters for monitoring ("what to monitor?"); 2. Monitoring methods, baselines including reference points, and duration of monitoring ("how to monitor?"); 3. Monitoring sites and regions ("where to monitor?"); 4. Reporting of monitoring results ("how to communicate?"). Where changes have been detected within a GS monitoring activity, the change needs to be linked to causal factors, which again may require additional research, and/or CSM monitoring. The issue of monitoring of GM animals released into the environment, much like other GMOs, is a critical element of risk assessment and management. Unlike GM plants, and particularly crop plants, GM animals have the added features of active mobility and spread, sometimes combined with intentional release into unmanaged ecosystems. This adds new dimensions to the risk assessment, particularly related to i) the stringency of sterility systems, ii) gene x environment interactions, and iii) potentially irreversible changes to ecosystems. Beyond the consideration of the PMEM monitoring guidance developed for GMPs under EFSA, these factors should be more explicitly dealt with in the guidance on GM animals, and particularly for monitoring. See "Part III: Monitoring of living modified organisms released inot the enivornment" http://bch.cbd.int/onlineconferences/guidance_ra/monitoring.shtml
192	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.3 Choice of comparators	ACRE notes that specific subheadings are included for fish and insects in this section. It does not, however, appear that the first section (lines 854-962) applies only to mammals and birds. This section provides consideration of the specific situation where a GM animal will be released to an environment where the wild type animal does not exist (lines 888-932). ACRE notes that the primary risk in such situations will result from the presence of an alien species, rather than specifically due to the genetic modification. As stated in lines 914-915, environmental risks of the animal, including the genetic modification, need to be considered as a package. The guidance should be amended to emphasise this point, rather than focussing on the issue of the lack of an unmodified comparator. For some types of animal, the introduction of an alien species is covered by existing legislation. To clarify this, the text at line 908 should be expanded to read "....invade this and other similar environments (EC, 2007), and therefore subject to regulation under EC Regulation No 708/2007 concerning the use of alien and locally absent species in aquaculture." It should be noted that a risk analysis scheme has been developed for assessing species under this regulation. ACRE considers it would be appropriate to use such existing regulatory frameworks to assess the environmental risks of introducing a GM animal into a new environment where the wild type comparator is not present. For some types of animal there is no existing legislation governing the introduction of alien species to a new environment. This is not, however, an issue which is specific to the introduction of genetically modified animals. ACRE considers that the guidance provided in lines 933-939 should be clearer and that this should not involve introducing a non-GM surrogate into the environment for purposes of conducting the study. The primary risk arises from the introduction of the animal and not from the genetic modification (see also comments on section 3.4). ACRE considers that changes in management practice (lines 950-962) should only be considered if these are needed specifically as a result of the genetic modification. This should be set in the context of wider changes to management practice, which can occur for a variety reasons other than

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				the introduction of a genetically modified organism. In some cases such changes would be restricted by other regulatory frameworks. Where this is not the case it may not be appropriate to impose different standards under the GM legislation. Possibly relating to this, the meaning of lines 954-957 requires clarification.
193	GenØk - Centre for biosafety	NOR	4.2.1 Persistence and invasiveness, including vertical gene transfer	Normative judgments related to the risk assessment The proposed risk assessment guidelines for genetically modified animals misappropriate the responsibility for normative judgments of risk within the assessment. For example, combining problem formulation into step 1 of the conduct of a risk assessment as proposed on lines 2973 and 3110 becomes problematic since the critical contextualizing and scoping outcomes, which do contain normative elements of protection goals and assessment endpoints, should be separated from the downstream conduct of the risk assessment. This is for the very good reason that the outcomes from the preliminary phase will guide and direct the RA into the appropriate measure to be considered in the RA itself. It is necessary to broaden the scope of the problem formulation by involving risk assessors, risk managers and interested/affected actors . The problem formulations phase should be a process that also is contextualised, so that the ERA includes protection goals and assessment endpoints considered important and that take into account national and/ or regional conditions. Further, the normative judgments of “significance” of harms and “acceptability” risks are misappropriated within the guidance. For example, under “Step 6: Overall risk evaluation and conclusions”, the guidance relates: “Applicants should conclude on the relative significance and acceptability of any associated environmental harm.”(See line 2766). In our opinion, “significance and acceptability of any associated environmental harm” are political decisions to be taken, not by the Applicant and not as part of the scientific evaluation of environmental risks, but within the larger context of decision-making. The transfer of responsibility of normative judgments related to risk to the Applicant, rather than to the competent authority, is erroneous and not an appropriate role for the Applicant. The guidance should better outline what critical normative elements are to be considered, by whom, and thereby how their determinations should influence the assessment.
194	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.2 Experimental environment	The link to problem formulation, and also to the previous section (3.1), needs to be clearer. It is important that the guidance does not assume that field trials will always be needed for purposes of ERA. This will depend on the nature of the modification. the first two paragraphs of this section require revision to clarify their meaning (lines 793-813). ACRE disagrees with the statement that the mobility of animals exceeds that of plants or a substance. Animals may exhibit more complex movement patterns, but this text does not reflect the potential of plants and substances to disperse and reach new locations. ACRE does not agree with the statement that the tiered approach has less relevance for the ERA of GM animals (line 813), which is the basis for following paragraphs in this section (lines 814-852).
195	GenØk - Centre for biosafety	NOR	Terms of reference as provided by the European Commission and EFSA	Ethical and socio-economic issues: The “EFSA Guidance document on the environmental risk assessment of genetically modified animals” does not take into account any aspects on information on the social utility of GM animals and its contribution to sustainable development (page 6). Ethical aspects are also not included. One important issue of ethics is related to animal welfare, involving mental/emotional and physical health of the individual animal or the animal’s living conditions. The term also includes behavior, as well as physiological and immunological factors. The Norwegian Animal Welfare Act of 2010, states that animals have an intrinsic value. This term contributes to clarifying that animal welfare must be prioritized irrespective of the value the animal may have for people, which also contributes to clarifying the animal’s status. GenØk is of the opinion that this kind of information should be integrated in the guidance document to be able to make sure that GM animals comply to animal welfare, that GM animals involve a benefit to the community and a contribution to sustainable development. The guidance document should make sure that there will be necessary data in order to conduct a thorough assessment on this issue.

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196	GenØk - Centre for biosafety	NOR	2. Strategies for the ERA of GM animals	The concept of familiarity: In the guidance, in chapter two, the concept of familiarity decides whether statistically significant differences in unintended ecological effects need to be assessed through ERA.or if they can be declared as biologically irrelevant. The comparators on which such decision are based are not necessarily the unmodified parental organisms – as required by EU legislation - but a range of currently used, foreign or other varieties which gives a description of the amount of knowledge and experience available. The Guidance does not indicate which varieties and tests that have to be used to assess "familiarity". GenØk is of the opinion that the concept is therefore vague. Moreover GenØk is of the opinion that familiarity should not be used as an upstream assessment point of safety.
197	NATIONAL COMMISSION ON BIOSAFETY, MINISTRY OF AGRICULTURE, FOOD AND ENVIRONMENT	ESP	3.3 Choice of comparators	Chapter 3, Section 3.3: The document develops sub-sections for Choice of Comparators for ERA of GM fish (3.3.1.) and GM insects (3.3.2) but a sub-section for Choice of Comparators for ERA of GM mammals and birds is missing. Why this has not been considered into this Chapter?
198	Advisory Committee on Releases to the Environment (ACRE)	GBR	3.1 Receiving environments	The inclusion of the term accessible ecosystem (replacing geographic zone in the plant guidance) is useful in making it clear that consideration of receiving environments should take routes of exposure into account. ACRE considers, however, that in general the guidance could make it clearer that the receiving environment should be considered specifically in the context of problem formulation. The need for this is particularly apparent in the section which refers to management systems (lines 704-722). It should not be implied that it is always necessary to characterise a full range of management systems, consider the use of by-products of the GM animal or associated pests and pathogens. The need for this will depend on the nature of the genetic modification. The 'selection of receiving environments' section (3.1.3) makes the link between problem formulation and receiving environments, but this uses language ('issue of concern') which is not used elsewhere in the document. The clarity of this point could be improved by using consistent terms throughout the guidance.
199	Advisory Committee on Releases to the Environment (ACRE)	GBR	3. Cross-cutting considerations	In general, this chapter lacks proportion because it endeavours to deliver scientifically robust and comprehensive guidance without consideration of the chapters where this information will be used to inform the ERA. It is not easy for the reader to determine how this section of the guidance should be used in combination with the three chapters on specific types of GM animal. ACRE notes that this section has been amended and further developed relative to that provided in the guidance on the ERA of GM plants.
200	Advisory Committee on Releases to the Environment (ACRE)	GBR	2.1 Different steps of the Environmental Risk Assessment	Section 2 sets out the framework used throughout the guidance. ACRE notes that the six step risk assessment used in the guidance differs from that set out in Directive 2001/18/EC. ACRE considers that the approach used in the guidance, of separating problem formulation, hazard and exposure identification and risk characterisation, overstretches the risk assessment process. This becomes apparent in the degree of repetition in the later chapters on the three types of animal, where each of the six steps is repeated for each 'area of risk.' Making use of a simpler three step process of hazard identification, risk assessment and risk management would help to address this without reducing the efficacy of the ERA. ACRE discusses this further later in this document in its comments on chapter 4. ACRE considers that the guidance should clearly state that risk assessment begins with identification of characteristics which may cause adverse effects. This should be based on the characteristics of the parent organism, the nature of the genetic modification and a characterisation of the genetically modified organism. Although these concepts are present in the guidance, they are not given sufficient emphasis. For example, ACRE considers that lines 360-362 and 419-422 detract from this central message and are not a useful addition to the guidance. ACRE considers that the scope of the guidance should be restricted to considering issues which arise because of the genetic modification. It is not appropriate for the guidance to extend to wider issues, which would not otherwise be regulated. For example in Section 2, on strategies for ERA of GM animals, it is stated that applicants should provide estimates of effluents generated by GM animals in the specified management and production systems (lines 478-479). This would only be necessary if the ERA identified a specific risk resulting from the genetic modification and should not therefore be a de facto requirement.

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201	GM Freeze	GBR	5. Post-Market Environmental Monitoring plan	Lines 6389 -6547 The Guidance sets out the wording in Directive 2001/18 on Case-Specific Monitoring (CSM) and General Surveillance (GS) to identify the occurrence of adverse effects of the GMO or its use on human health or the environment which were not anticipated in the ERA. This sets out what PMEM is intended to achieve: to confirm that the risk assessment was correct and to detect unanticipated consequences of the release of a GM animal. Post Market Environmental Monitoring is therefore not intended to fill data gaps that should have been provided in the risk assessment. If it proves impossible to provide adequate data without first releasing the GM animal into the environment, then the correct course of action under the precautionary principle is to reject an authorisation to release until the gaps are adequately filled and scientific uncertainties resolved.
202	GM Freeze	GBR	4.3 Specific areas of risk for the ERA of GM mammals and birds	Line 4368-6387 The Draft Guidance document distinguishes between GM animals which are captive, semi-captive and non-captive. It is worth reiterating that there is a well documented history of captive animals and birds escaping into the wild either as a result of carelessness, neglect or deliberate intervention by third parties. Species that have escaped and become established in the UK are numerous and include mammals (eg, American mink, coypu, muskrat, three species of deer, edible dormouse and red necked wallaby), reptiles (eg, the European Pond terrapin), birds (eg, ruddy duck, eagle owl, ringed neck parakeet and Canada Goose), amphibians (eg, American bull frog, marsh frog and European tree frog), molluscs (eg, zebra mussel and slipper limpet) and crustaceans (eg, signal crayfish). The means of escape or release of these species are largely known, but this does not necessarily lead to greater biosecurity aimed at preventing future releases. Some species (eg, coypu, muskrat and ruddy duck) have been successfully eliminated or controlled by culling programmes, but others (eg, American mink, Canada geese and Muntjac deer) continue to thrive. The environmental and economic impacts of introduced species is also highly variable, from very serious in the case of North America mink or fish farms and fisheries, to none known in the case of the European Pond Terrapin (see Introduced Species into the UK website www.introduced-species.co.uk/index.htm). The success of escaped or released GM animals will depend on how well they are adapted, or adapt to, local conditions as they disperse. The difficulties in establishing this prior to approval are huge and ultimately will depend of the quality and quantity of the data collected. The Draft Guidance document puts forward four case studies. Two of these are said to be “in an advanced stage of development” – the Enviropig and flu resistant chicken (lines 4375-4377). However development of the former has now ended (see www.huffingtonpost.ca/2012/06/21/enviropigs-university-of-guelph_n_1617140.html), so it is hardly a good example. Other cases studies are either dependent on further development (avian flu resistant chickens) or are theoretical (the sterile rabbit and the growth enhanced cat). Neither of the case study animals cited as examples was used systematically to demonstrate the approach to risk assessment proposed in the Guidance, so it is not clear what value the case studies provide. The use of some detailed cases studies may provide greater clarity about the complexity of what is involved in assessing the risks of any GM animal. The case of the sterile rabbit being used to control wild rabbit populations could be usefully employed to do this and to illustrate the far-reaching consequences such an application of GM technology might have. These would include indirect effects (such the potential loss/reduction of rabbit grazing on sensitive grassland habitats), the impacts of reduced food availability on wild predators and their other prey species (including carrion eaters) and the economic impacts of the widespread reduction in rabbit populations.

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203	Advisory Committee on Releases to the Environment (ACRE)	GBR	2. Strategies for the ERA of GM animals	ACRE welcomes EFSA's efforts to develop a structured framework for environmental risk assessment in this new and emerging area. Significant revision of this draft will, however, be needed before this guidance can be used effectively by applicants and regulators. ACRE's view is that the guidance should provide a framework to help applicants construct an ERA. It should not be prescriptive but should be sufficiently flexible to capture a range of GM animals and their uses. EFSA's inclusion in its guidance of concepts that facilitate a systematic approach to the ERA of GM animals is therefore a positive step. At present, however, the guidance presents too great a level of detail. As a result the focus appears to be on a rather burdensome procedure with little recognition that in most cases there will only be a science-based rationale for the existence of a restricted range of environmental hazards. The guidance includes detailed discussions of factors which might contribute to risk in specific cases that the reader is not helped to rationalise. Attempting to provide an exhaustive consideration of all potential risks obscures the risk assessment framework. The guidance seeks to be fully comprehensive, but for any case-specific risk assessment, this will not be possible. By taking this approach there is the potential that applicants will focus on the risks identified in the guidance and that risks which were not identified will be neglected. The final version of this guidance should place greater emphasis on developing a high level framework for ERA, which assists applicants in identifying and characterising risks on a case by case basis. The emphasis needs to be placed more firmly on problem formulation being used to determine the scope of the ERA which is needed. The tiered testing approach needs to be more apparent and to achieve this, the consistent inclusion of decision trees throughout the guidance would be beneficial. To support this structured framework, ACRE recommends the inclusion of a small number of separate, specific worked examples to illustrate how this approach would be used in practice.
204	GM Freeze	GBR	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Lines 4091-4093 The draft guidance includes the following sentence in relation to the management of GM insects: "Alteration to management practices might provide both environmental benefits as well as harm so that the net environmental impact of the overall production system needs to be considered". It is unclear why an analysis of "benefits" is included because the assessment of environmental benefits is not covered by the mandate to EFSA provide by the European Commission on 13 February 2007 and 25 March 2010. Neither are environmental benefits mentioned in Directive 2001/18 and it annexes. Other sections of the Draft Guidance on GM fish and animals do not include any reference to environmental benefits. GM Freeze believes this it is outside EFSA's remit to consider benefits as the aim of the environmental risk assessment is "for the safety assessment of GM animals that would address both food and feed and environmental safety as well as animal health and welfare issues" (lines 167-168). The assessment of environmental benefits should be undertaken in a separate process, as with ethics and socio-economic impacts of the GM animal.
205	GM Freeze	GBR	4.2 Specific areas of risk for the ERA of GM insects	Lines 1818-1822 This section acknowledges the need for a risk assessment of GM honeybees. Whilst GM Freeze agrees that the welfare of honeybees is vitally important, we would oppose the use of genetic modification to address any of the serious problems which are currently harming their populations across the EU which include disease, parasites and exposure to pesticides such as the nicotinoids, nor are we convinced such impacts are restricted to honeybees alone among pollinators. Rather than addressing the welfare implications of GM honeybees, there is an overriding need to improve the welfare of existing populations of all pollinators. With regard to honeybees, this should include the potential role that inbreeding of new strains of honeybees has played in their susceptibility of honeybees to diseases, parasites and other threats and the effectiveness of biosecurity measures to prevent the arrival on new diseases or parasite or new strains of the same. The genetic modification of bees could reduce apian genetic diversity at a time when a larger gene pool may be required to regenerate more robust colonies. GM Freeze rejects the idea of genetically modifying honeybees to be tolerant insecticide because it completely ignores the threat this would pose to other wild pollinators will not carry this GM trait from continued use of harmful insecticides.

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206	GM Freeze	GBR	3.8.3 Health and welfare aspects for GM insects	Lines 1818-1822 This section acknowledges the need for a risk assessment of GM honeybees. Whilst GM Freeze agrees that the welfare of honeybees is vitally important, we would oppose the use of genetic modification to address any of the serious problems which are currently harming their populations across the EU which include disease, parasites and exposure to pesticides such as the nicotinoids, nor are we convinced such impacts are restricted to honeybees alone among pollinators. Rather than addressing the welfare implications of GM honeybees, there is an overriding need to improve the welfare of existing populations of all pollinators. With regard to honeybees, this should include the potential role that inbreeding of new strains of honeybees has played in their susceptibility of honeybees to diseases, parasites and other threats and the effectiveness of biosecurity measures to prevent the arrival on new diseases or parasite or new strains of the same. The genetic modification of bees could reduce apian genetic diversity at a time when a larger gene pool may be required to regenerate more robust colonies. GM Freeze rejects the idea of genetically modifying honeybees to be tolerant insecticide because it completely ignores the threat this would pose to other wild pollinators will not carry this GM trait from continued use of harmful insecticides.
207	GM Freeze	GBR	3.8.2 Health and welfare aspects for GM fish	Lines 1798 – 1817 GM fish are most likely to be produced for intensive production facilities, which already form the basis for aquaculture in the EU. These involve keeping fish at naturally high densities and carry a high risk of increased disease and parasites, all of which increase the use of antibiotics and subsequent waste discharge into surrounding ecosystems and resulting damage. Genetically modified fish are likely to exacerbate these problems, as it is likely to reduce the genetic base of farmed stock. GM animals so far proposed include fast growing Atlantic salmon from the US company AquaBounty. Fast GM growing fish could be to subject to fitness and behaviour problems, as has been the case in other groups such as broiler chickens (which have also been selectively bred to grow quickly, and where lameness and heart problems are subsequently common – see Compassion in World Farming www.ciwf.org.uk/farm_animals/poultry/meat_chickens/welfare_issues.aspx).
208	GM Freeze	GBR	3.8.1 Health and welfare aspects for GM mammals and birds	Lines 1769 -1797 GM Freeze emphasises that animal welfare is of paramount importance. The Draft Guidance rightly points out that existing breeding of birds and mammals has increased welfare problems in many groups such as dairy and beef cattle, broiler chickens, turkeys and dogs. Genetic modification could exacerbate existing conditions or introduce new problems. The cloning of GM mammals and birds would add to welfare problems, as the record in cloned farm animals is very poor in this respect. GM Freeze therefore believes that issuing a risk assessment Guidance is unwelcome as it will only serve to encourage developments of GM animals in the absence of any need, demand or convincing means to adequately assess their impact
209	GM Freeze	GBR	3.8 Aspects of GM animal health and welfare	Lines 1738-1823 GM Freeze considers that the welfare of animals should be a high priority. The Draft Guidance correctly indicates that animal welfare has been the subject of legislation in the EU. This should apply to all GM animals, and welfare should be used as a reason for refusing any application to produce, release or market GM animals. We believe that the introduction of a Draft Guidance for the risk assessment of GM animals is premature and should not be progressed until there has been a full and wide-ranging debate on GM animals across the EU, including examining the necessity of such a development.
210	GM Freeze	GBR	3.7.3 Interplay between ERA conclusions and PMEM	Lines 1721 -1737 The drafting of this section leaves a lot to be desired. “the ERA is often constrained/restricted by the available knowledge and experience of the GM animal and it can be difficult to predict and consider all potential future applications, production systems and receiving environments of the GM animal. Thus large-scale and long-term use of a GM animal could result in some effects which were not predictable at the time of the ERA or consent. Therefore, according to Directive 2001/18/EC (EC, 2001), applicants are required to conduct general surveillance (GS) to detect unanticipated adverse effects on the environment”. This gives applicants the option to rely on post market environmental monitoring (PMEM) to file gaps in data. We reject this approach in favour of one based upon the precautionary principle, under which environmental protection would take precedence over premature approval of a GM animal where data on its impacts were inadequate.

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211	GM Freeze	GBR	3.7 Uncertainty analysis	Lines 1549-1720 This section of the Draft recommends various techniques and approaches in dealing with uncertainty in the risk assessment for GM animals. While all the proposed methods are valid, none provides an adequate approach if data on the GM animal is absent or inadequate to use in any of the techniques. What is lacking in this section is any guidance as to what applicants or regulators should do if the uncertainty analyses do not provide sufficient certainty or even adds to the uncertainty. The absence of any guidance as to when and how the precautionary principle should be applied in this section, or indeed the entire document, is therefore a major oversight or omission. Given that the precautionary principle underpins Directive 2001/18, this is unacceptable.
212	GM Freeze	GBR	3.6 Long-term effects	Lines 1498-1505 “Long-term effects of category II, by definition, cannot be investigated through an initial experimental phase of testing, as none of the possible experimental design can provide the range of complexity experienced after full commercial release. For example, it is likely to be difficult to mimic, with a confined experimental set up, all conditions occurring in the receiving environments in order to assess possible interactions of a GM animal with other animal species. Category II effects can only be investigated by reference to possible existing examples and case studies that provide evidence of rates and magnitudes of environmental impact due to change in production systems (e.g. intensive grazing) or external (e.g. climate change) factors”. As is clear from this extract from the Draft Guidance, experimental design to test if the releases of GM animals are likely to result in significant ecological changes to the receiving ecosystem are very difficult to design and carry out. Experiments should be powerful enough to detect such differences, especially those which are cumulative in nature and could be missed by shorter, less powerful experiments. In a 25-year field study of food supply for farmland birds in the UK, difference in weed abundance (weed seed is an important food source) detected difference of 13% (P <0.001) and were ecological significant (Ewald J.A. and Aebischer N.J., 1999. “Pesticide use, avian food resources and bird densities in Sussex”, Joint Nature Conservation Committee Report No 296; page 70). This emphasises how easy it would be to miss such differences in GM animal experiments that are poorly designed or are too limited in their power. Line 1521 Meta-analysis is recommenced when there is a lack of sufficient data or conclusive data in any study. Meta-analysis is based on combining the results of several different studies. However this approach is not without its problems (eg, bias caused by applicants selecting studies showing favourable, rather than unfavourable, results or the selection of inappropriate studies included because there are so few appropriate ones available). In the case of GM animals meta-analysis is most likely based on studies of comparators or appropriate surrogates to the GM animal. GM Freeze is concerned that this could result in reliance on inappropriate studies given the difficulties outlined above concerning the selection of comparators or surrogates. This adds weight to the argument that the approval of GM animals is premature, and taken with other factors such as ethics and socio-economic factors should mean a ban.
213	GM Freeze	GBR	3.4 The use of non-GM surrogates	Lines 1052-1107 The use of non-GM surrogates as a comparator in ERAs is not recommended by GM Freeze. For example GM insects with the female lethality gene and sterile insects induced by radiation would not be directly comparable as the former result in fertile eggs being laid and hatching but failing to mature to adulthood, while the latter do not produce any offspring. Each system has a different failure rate, and in the case of Oxitec’s GM mosquito developed to control Dengue Fever, the lethality gene can be switched off by the presence of the chemical trigger in the environment (in this case the antibiotic tetracycline). In sterile insect technology, the sterility cannot be reversed once it is achieved, although fertile individuals can still be produced. In the case of AquaBounty’s fast growing salmon, which is currently undergoing regulatory approval in the US, no obvious surrogate stands out. The GM fish cannot be released into the wild without the possibility of interference with native populations and causing irreversible damage. The use of completely different species is fraught with difficulties, as illustrated by the behaviour differences between Rainbow and Brown Trout above. The introduction of any new species into an aquatic ecosystem can alter the behaviour of native stock, for instance research has shown that wild juvenile Brown Trout responded to the presence of predatory adult Brown Trout by seeking refuges more often. However this behaviour was not observed in second generation hatchery fish, which were far less responsive to predation (Alvarez D. and Nicieza A.G., 2003. “Predator avoidance behaviour in

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				wild and hatchery-reared brown trout: the role of experience and domestication". Journal of Fish Biology 63: 1565–1577). This only serves to illustrate the difficulties in trying to model in "controlled" conditions the short-term and long-term consequences of aGM fish escape into the wild. In our view knowledge gaps relating to the interactions of GM animals in the natural environment will be significant because of the difficulties of conducting controlled experiments, and therefore the Guidance should explicitly state that the precautionary principle should apply where such gaps exist and applications should not be approved.
214	GM Freeze	GBR	2. Strategies for the ERA of GM animals	Lines 286-325 GM freeze has concerns about the lack of attention payed by the Draft Guidance to ensuring that baseline data on ecosystems into which GM animals are to be released is fully available and understood. This will be needed to enable the complex interrelationships of the food webs above and below ground to be fully understood and increase the chances of being able to design trials or models to test hypothesis as to the possible impacts of a GM animal. Baseline data should extend to all seasons and abiotic conditions to ensure that all possible interactions between resident species and the existing ecosystems are understood, enabling the possible impact of the accidental or deliberate introduction of a GM animals to be assessed. Lines 555-559 GM Freeze would like to emphasise that Post Market Environmental Monitoring (PMEM) must not be used to fill knowledge gaps or to clarify uncertainties that have not been addressed by the risk assessment for GM animals. The history of the deliberate or accidental release of animals into new environments shows that the results can be unpredictable and may take many decades to fully develop. For example, Pacific salmon which migrated from Russian rivers feeding the White Sea in the 1960s, have only recently started to appear in Scottish rivers (eg, the Tweed, see Association of Salmon Fishery Boards 2011 www.asfb.org.uk/pacific-salmon-species-caught-in-tweed-district/). The consequences of such arrivals on native fish stocks are not yet clear and may not be obvious for a number of years because, for instance, they may be dependent on the alien species adapting to local conditions or reaching critical population thresholds. Removing GM animals from ecosystems to which they are or have become well adapted could prove to be very difficult, as it has with many previous escapes or introductions (see for instance the case of the Zander (Linfield R S J, undated. The impact of Zander (Stizostedion lucioperca (l.)) in the United Kingdom and the future management of affected fisheries in the Anglian Region (FAO www.fao.org/docrep/009/ae997b/AE997B09.htm#TopOfPage).
215	GM Freeze	GBR	Assessment	Line 229 It is unclear why the Guidance document exclude GM animals to produce pharmaceuticals when these will pose a potential threat to the environment as well as clearly raising additional safety issues because of the presence of biologically active GM products. GM Freeze believes that GM animals producing pharmaceuticals should therefore be covered by this Guidance in addition to the usual pharmaceutical safety assessments. Lines 248-252. The Guidance document fails to make a clear distinction between experimental and commercial releases. In the case of GM insects experimental releases will often be designed to demonstrate commercial viability and therefore involve the releases of millions of GM insects (as was the cases with Oxitec's recent releases of GM mosquitoes in the Cayman islands, Malaysia and Brazil). The need for a rigorous risk assessment is as great for such trials as for full commercial releases. EFSA should address this point in the final Guidance document. Lines 283-285 The document highlights the release of non-captive GM animals, such as insects and rabbits modified to control problem wild populations, into "specific environments". GM Freeze suggests that this should refer to "the environment" because the possibility of GM animals being confined to a specific environment is extremely unlikely in most cases and damage to ecosystems they inhabit could be significant.

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216	GM Freeze	GBR	Background as provided by the European Commission and EFSA	Lines 164-193 It is very unclear why EFSA has been asked to embark on developing risk assessment Guidance for GM animals at a time when there seems to be very little prospect of them finding a market in the EU because of the widespread public opposition to over forms of GM technology in crops and the cloning of animals in the EU. The only credible explanation is that industry has pressed for this to demonstrate GM animal research and development is not a blind alley in the hope of satisfying existing investors and staying in business long enough to encourage new ones. Line 187 The genetic modification of animals raises new ethical and moral issues that should result in the rejection of the technology in the EU. The Draft Guidance is therefore premature as it should follow a wide ranging debate across the EU as to whether GM animals are acceptable. Issues such as the treatment of animals as commodities rather than sentient beings would feature strongly in such a debate. GM Freeze believes that this document must follow such a debate rather than preceding, and possibly pre-empting, it.
217	GM Freeze	GBR	Abstract	The abstract should acknowledge that the Environmental Risk Assessment (ERA) is but one part of the assessment of GM animals and that ethical, socio-economic and welfare considerations also form an equal part of the overall assessment and should lead to the outright rejection of the genetic modification of the animals in the EU for any purpose.
218	Max-Planck-Institut für Evolutionsbiologie	DEU	5. Post-Market Environmental Monitoring plan	Line 6389: Advice on post-Market Environmental Monitoring Plans might be too generic to be useful for such a broad range of potential applications. Having a separate section for each of the 3 taxonomic groupings considered might be a good idea.
219	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3 Specific areas of risk for the ERA of GM mammals and birds	Line 4402: It should be clarified for readers that sons do inherit the transgene from their fathers but that it is only functionally expressed in females.
220	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:-EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.

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221	Max-Planck-Institut für Evolutionsbiologie	DEU	5.1 Case-Specific Monitoring (CSM)	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. t is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.
222	Max-Planck-Institut für Evolutionsbiologie	DEU	5.2 General Surveillance (GS)	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? t he only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.

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223	Max-Planck-Institut für Evolutionsbiologie	DEU	5. Post-Market Environmental Monitoring plan	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN.http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.
224	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.

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225	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN.http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- ‘Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.’ Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.
226	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- ‘Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.’ Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.

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227	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.
228	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.

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229	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN Htp://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.
230	Max-Planck-Institut für Evolutionsbiologie	DEU	Summary	Line 4249: Does the EFSA consider that allergenic risks associated with the blood feeding of insects can be adequately assessed using procedures developed to assess the allergenic potential of eating GM plants? The only document cited for the experiment assessment of allergenicity is:- EFSA GMO Panel Scientific Opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed. Group 1–163 (2010).doi:10.2903/j.efsa.20NN.NNNN. http://www.efsa.europa.eu/fr/efsajournal/pub/1700.htm However, this document is exclusively focused on the allegenicity of ingestion, it has nothing to say on allergens injected into the blood. Mosquitoes inject approximately 40 proteins as part of a natural bite and there is a theoretical risk that any GM expressed proteins in the salivary gland could also be injected (regardless of whether or not they included a secretion signal sequence). It is interesting to consider how well the approach outlined in the cited document above would perform in determining that while most people could eat a bee with no effect, having bee venom injected as part of a sting can produce a strong reaction in some rare individuals. It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance.

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231	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
232	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.2 Step 2: Hazard characterisation	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified

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				Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
233	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.3 Step 3: Exposure characterisation	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
234	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.4 Step 4: Risk characterisation	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
235	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.5 Step 5: Risk management strategies	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). t is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502

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				3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
236	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.6 Step 6: Overall risk evaluation and conclusions	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043

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237	Max-Planck-Institut für Evolutionsbiologie	DEU	2.2 Information to identify potential unintended effects	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
238	Max-Planck-Institut für Evolutionsbiologie	DEU	2.3 Structural overview of this Guidance Document	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that: 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf>

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				2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
239	Max-Planck-Institut für Evolutionsbiologie	DEU	2. Strategies for the ERA of GM animals	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.

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240	Max-Planck-Institut für Evolutionsbiologie	DEU	3. Cross-cutting considerations	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
241	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf>

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
				2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
242	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
243	Max-Planck-Institut für Evolutionsbiologie	DEU	5.1 Case-Specific Monitoring (CSM)	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
244	Max-Planck-Institut für Evolutionsbiologie	DEU	5.2 General Surveillance (GS)	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf>

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245	Max-Planck-Institut für Evolutionsbiologie	DEU	5. Post-Market Environmental Monitoring plan	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
246	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
247	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf>

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248	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
249	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
250	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
251	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:- 'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at <http://www.efsa.europa.eu/en/supporting/doc/71e.pdf> 2 Reeves, R. G., Denton, J. A., Santucci, F., Bryk, J. & Reed, F. A. Scientific standards and the regulation of genetically modified insects. PLoS neglected tropical diseases 6, e1502 (2012). http://dx.plos.org/10.1371/journal.pntd.0001502 3 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0836-0043.
252	Max-Planck-Institut für Evolutionsbiologie	DEU	Summary	Line 4242 and whole document: Why is the consideration of the hazards arising from the deliberate or unintentional exposure to blood feeding GM insects entirely absent from this document? This omission is remarkable given its discussion in the draft document (pages 97-98, 135 Umweltbundesamt 2010(1), its prominence in the general media e.g. during the 2012 proposed release of GM mosquitoes in Florida (USA), and also the scientific literature (2). Given the concern about this issue in relation to techniques with limited opportunity for individuals to opt-out of exposure it would be useful to discuss whether the experimental assessments of this hazard might be something that might need to be validated independently. Though this could be impeded by lack of access to relevant living biological material without onerous restrictions for independent researchers (3). It is notable that while in the bird and mammal section applications are advised that:-'Applicants shall take particular care over this allergenic assessment if any new (recombinant) protein is expressed in dander, saliva or urine.' Line 6329 Surprisingly, similar advice with respects to salivary fluids, which are injected as part of a normal mosquito bite, is not given in the insect section despite its obvious relevance. A clear discussion of obvious concerns stemming from the presence of female GM mosquitoes in the environment should be as a commitment to resolve all realistic concerns in an appropriate scientific forum and should not necessarily be seen by anybody as a legitimisation of their scientific basis (see comment to line 14) 1 Umweltbundesamt Scientific / Technical Report submitted to EFSA. Defining Environmental Risk Assessment Criteria for Genetically Modified Insects to be placed on the EU Market . 200 (2010).at http://www.efsa.europa.eu/en/supporting/doc/71e.pdf

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253	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 4275 (d) and its connection to line 4205 (d): If the list of concerns (a)-(g) starting on line 4177 are supposed to be correspondingly discussed in the list (a)-(g) starting 4328 then there is an important error in point (d). There is not a correspondence the concern described in (d) line 4205 is not discussed adequately in the document. Line 4205-4206 (d) clearly sets out the hazard associated with inadvertent selection for increased virulence or morbidity of the target pathogen during population replacement strategies. This concern has been repeatedly discussed for GM replacement strategies (e.g. (1,2), but also in the context of vaccine (3) and Wolbachia releases (4). However, the characterisation of the corresponding hazard on line 4275 to 4284 (d) discusses a completely unrelated hazard. This obvious mistake should be corrected and this important and complex issue should be properly discussed. 1 Medlock, J., Luz, P. M., Struchiner, C. J. & Galvani, A. P. The impact of transgenic mosquitoes on dengue virulence to humans and mosquitoes. The American naturalist 174, 565–77 (2009). 2 Andow, D. A. Risk Assessment of LM Mosquitoes bch.cbd. at http://bch.cbd.int/database/record.shtml?documentid=101015 3 Mackinnon, M. J. & Read, A. F. Immunity promotes virulence evolution in a malaria model. PLoS biology 2, E230 (2004). 4 Murphy, B., Jansen, C., Murray, J. & De Barro, P. Risk Analysis on the Australian release of Aedes aegypti (L.)(Diptera: Culicidae) containing Wolbachia. CSIRO. PAGE 59 (2010).at http://www.eliminatedengue.com/Portals/58/PDFs/NEW-Risk Analysis of proposed Wolbachia Aedes aegypti release Final Report for public release 9 March 2010.pdf
254	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 4275 (d) and its connection to line 4205 (d): If the list of concerns (a)-(g) starting on line 4177 are supposed to be correspondingly discussed in the list (a)-(g) starting 4328 then there is an important error in point (d). There is not a correspondence the concern described in (d) line 4205 is not discussed adequately in the document. Line 4205-4206 (d) clearly sets out the hazard associated with inadvertent selection for increased virulence or morbidity of the target pathogen during population replacement strategies. This concern has been repeatedly discussed for GM replacement strategies (e.g. (1,2), but also in the context of vaccine (3) and Wolbachia releases (4). However, the characterisation of the corresponding hazard on line 4275 to 4284 (d) discusses a completely unrelated hazard. This obvious mistake should be corrected and this important and complex issue should be properly discussed. 1 Medlock, J., Luz, P. M., Struchiner, C. J. & Galvani, A. P. The impact of transgenic mosquitoes on dengue virulence to humans and mosquitoes. The American naturalist 174, 565–77 (2009). 2 Andow, D. A. Risk Assessment of LM Mosquitoes bch.cbd. at http://bch.cbd.int/database/record.shtml?documentid=101015 3 Mackinnon, M. J. & Read, A. F. Immunity promotes virulence evolution in a malaria model. PLoS biology 2, E230 (2004). 4 Murphy, B., Jansen, C., Murray, J. & De Barro, P. Risk Analysis on the Australian release of Aedes aegypti (L.)(Diptera: Culicidae) containing Wolbachia. CSIRO. PAGE 59 (2010).at http://www.eliminatedengue.com/Portals/58/PDFs/NEW-Risk Analysis of proposed Wolbachia Aedes aegypti release Final Report for public release 9 March 2010.pdf

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
255	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 4275 (d) and its connection to line 4205 (d): If the list of concerns (a)-(g) starting on line 4177 are supposed to be correspondingly discussed in the list (a)-(g) starting 4328 then there is an important error in point (d). There is not a correspondence the concern described in (d) line 4205 is not discussed adequately in the document. Line 4205-4206 (d) clearly sets out the hazard associated with inadvertent selection for increased virulence or morbidity of the target pathogen during population replacement strategies. This concern has been repeatedly discussed for GM replacement strategies (e.g. (1,2), but also in the context of vaccine (3) and Wolbachia releases (4). However, the characterisation of the corresponding hazard on line 4275 to 4284 (d) discusses a completely unrelated hazard. This obvious mistake should be corrected and this important and complex issue should be properly discussed. 1 Medlock, J., Luz, P. M., Struchiner, C. J. & Galvani, A. P. The impact of transgenic mosquitoes on dengue virulence to humans and mosquitoes. The American naturalist 174, 565–77 (2009). 2 Andow, D. A. Risk Assessment of LM Mosquitoes bch.cbd. at http://bch.cbd.int/database/record.shtml?documentid=101015 3 Mackinnon, M. J. & Read, A. F. Immunity promotes virulence evolution in a malaria model. PLoS biology 2, E230 (2004). 4 Murphy, B., Jansen, C., Murray, J. & De Barro, P. Risk Analysis on the Australian release of Aedes aegypti (L.)(Diptera: Culicidae) containing Wolbachia. CSIRO. PAGE 59 (2010).at http://www.eliminatedengue.com/Portals/58/PDFs/NEW-Risk Analysis of proposed Wolbachia Aedes aegypti release Final Report for public release 9 March 2010.pdf
256	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 4275 (d) and its connection to line 4205 (d): If the list of concerns (a)-(g) starting on line 4177 are supposed to be correspondingly discussed in the list (a)-(g) starting 4328 then there is an important error in point (d). There is not a correspondence the concern described in (d) line 4205 is not discussed adequately in the document. Line 4205-4206 (d) clearly sets out the hazard associated with inadvertent selection for increased virulence or morbidity of the target pathogen during population replacement strategies. This concern has been repeatedly discussed for GM replacement strategies (e.g. (1,2), but also in the context of vaccine (3) and Wolbachia releases (4). However, the characterisation of the corresponding hazard on line 4275 to 4284 (d) discusses a completely unrelated hazard. This obvious mistake should be corrected and this important and complex issue should be properly discussed. 1 Medlock, J., Luz, P. M., Struchiner, C. J. & Galvani, A. P. The impact of transgenic mosquitoes on dengue virulence to humans and mosquitoes. The American naturalist 174, 565–77 (2009). 2 Andow, D. A. Risk Assessment of LM Mosquitoes bch.cbd. at http://bch.cbd.int/database/record.shtml?documentid=101015 3 Mackinnon, M. J. & Read, A. F. Immunity promotes virulence evolution in a malaria model. PLoS biology 2, E230 (2004). 4 Murphy, B., Jansen, C., Murray, J. & De Barro, P. Risk Analysis on the Australian release of Aedes aegypti (L.)(Diptera: Culicidae) containing Wolbachia. CSIRO. PAGE 59 (2010).at http://www.eliminatedengue.com/Portals/58/PDFs/NEW-Risk Analysis of proposed Wolbachia Aedes aegypti release Final Report for public release 9 March 2010.pdf
257	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6)

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258	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.2 Horizontal gene transfer	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
259	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.3 Interactions of the GM insects with target organisms	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
260	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.4 Interactions of the GM insect with non-target organisms	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
261	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6)
262	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
263	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
264	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).

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265	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of curent techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
266	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
267	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
268	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
269	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	LINE 2937 and whole of section 4.2: This section would be greatly improved for both non-specialists and specialists if the same example based approach used in the bird and mammal section was applied (section 4.3.). This need not impact on the applicability of the guidance to a wide range of current techniques and those developed in the future. It would however greatly enhance its clarity, particularly in the impact on human health section (4.2.6).
270	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.3 Interactions of the GM insects with target organisms	Line 3416 and rest of document: Shouldn't the possibility of introducing adaptive genes from the background of the release stock into the wild population be considered here? This has already proved to be one of the bigger concerns for regulators (e.g. UK, Malaysia) where foreign genetic backgrounds are used (particular in the context to insecticide resistance alleles, which are not linked to the transgene). I cannot see that this hazard is extensively discussed, which is surprising as most of the most problematic insect pests are difficult to control due to their capacity to adapt locally to fill any available niche and or become resistant to current control methods. While the document deals extensively with hazards resulting from transgenes it has very little consideration of the probable risks resulting from non-local backgrounds. While it is hard to firmly establish details due to the limited publication of details, it appears that many of the GM insects already released in experimental field trials have been using non-local genetic backgrounds. For example in Brazil and the Cayman islands the partially-sterile mosquitoes released are predominantly of Mexican origin, the species involved Aedes aegypti is well known for its capacity to adapt to insecticides and local conditions (e.g. http://www.cdc.gov/dengue/entomologyecology/index.html)

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271	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 3416 and rest of document: Shouldn't the possibility of introducing adaptive genes from the background of the release stock into the wild population be considered here? This has already proved to be one of the bigger concerns for regulators (e.g. UK, Malaysia) where foreign genetic backgrounds are used (particular in the context to insecticide resistance alleles, which are not linked to the transgene). I cannot see that this hazard is extensively discussed, which is surprising as most of the most problematic insect pests are difficult to control due to their capacity to adapt locally to fill any available niche and or become resistant to current control methods. While the document deals extensively with hazards resulting from transgenes it has very little consideration of the probable risks resulting from non-local backgrounds. While it is hard to firmly establish details due to the limited publication of details, it appears that many of the GM insects already released in experimental field trials have been using non-local genetic backgrounds. For example in Brazil and the Cayman islands the partially-sterile mosquitoes released are predominantly of Mexican origin, the species involved Aedes aegypti is well known for its capacity to adapt to insecticides and local conditions (e.g. http://www.cdc.gov/dengue/entomologyecology/index.html)
272	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 3416 and rest of document: Shouldn't the possibility of introducing adaptive genes from the background of the release stock into the wild population be considered here? This has already proved to be one of the bigger concerns for regulators (e.g. UK, Malaysia) where foreign genetic backgrounds are used (particular in the context to insecticide resistance alleles, which are not linked to the transgene). I cannot see that this hazard is extensively discussed, which is surprising as most of the most problematic insect pests are difficult to control due to their capacity to adapt locally to fill any available niche and or become resistant to current control methods. While the document deals extensively with hazards resulting from transgenes it has very little consideration of the probable risks resulting from non-local backgrounds. While it is hard to firmly establish details due to the limited publication of details, it appears that many of the GM insects already released in experimental field trials have been using non-local genetic backgrounds. For example in Brazil and the Cayman islands the partially-sterile mosquitoes released are predominantly of Mexican origin, the species involved Aedes aegypti is well known for its capacity to adapt to insecticides and local conditions (e.g. http://www.cdc.gov/dengue/entomologyecology/index.html)
273	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 3049: Citation of the Handler 2004 reference is probably a mistake, it has nothing to do with incomplete lethality/ vertical inheritance. The reference below (1) describes a system with appreciable survival due to incomplete lethality, there are others. 1 Phuc, H. K. et al. Late-acting dominant lethal genetic systems and mosquito control. BMC biology 5, 11 (2007).
274	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 3049: Citation of the Handler 2004 reference is probably a mistake, it has nothing to do with incomplete lethality/ vertical inheritance. The reference below (1) describes a system with appreciable survival due to incomplete lethality, there are others. 1 Phuc, H. K. et al. Late-acting dominant lethal genetic systems and mosquito control. BMC biology 5, 11 (2007).
275	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 3004: The largest unavoidable source of females is most likely from incomplete lethality of the GM construct (a recognised feature of some but not all developed systems), why is this not mentioned?
276	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure	Line 3004: The largest unavoidable source of females is most likely from incomplete lethality of the GM construct (a recognised feature of some but not all developed systems), why is this not mentioned?

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			pathways)	
277	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2980: Possible addition list (5) unintended long-term exposure of humans to transgene through ingestion and biting in some species?
278	Max-Planck-Institut für Evolutionsbiologie	DEU	1. Scope of this Guidance Document	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration
279	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
280	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.2 Step 2: Hazard characterisation	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
281	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.3 Step 3: Exposure characterisation	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
282	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.4 Step 4: Risk characterisation	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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283	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.5 Step 5: Risk management strategies	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
284	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1.6 Step 6: Overall risk evaluation and conclusions	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
285	Max-Planck-Institut für Evolutionsbiologie	DEU	2.1 Different steps of the Environmental Risk Assessment	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
286	Max-Planck-Institut für Evolutionsbiologie	DEU	2.2 Information to identify potential unintended effects	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
287	Max-Planck-Institut für Evolutionsbiologie	DEU	2.3 Structural overview of this Guidance Document	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
288	Max-Planck-Institut für Evolutionsbiologie	DEU	2. Strategies for the ERA of GM animals	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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289	Max-Planck-Institut für Evolutionsbiologie	DEU	3.1.1 Definition of receiving environments	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
290	Max-Planck-Institut für Evolutionsbiologie	DEU	3.1.2 Identification and characterization of the receiving environments	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
291	Max-Planck-Institut für Evolutionsbiologie	DEU	3.1.3 Selection of the relevant receiving environments	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
292	Max-Planck-Institut für Evolutionsbiologie	DEU	3.1 Receiving environments	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
293	Max-Planck-Institut für Evolutionsbiologie	DEU	3.2 Experimental environment	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
294	Max-Planck-Institut für Evolutionsbiologie	DEU	3.3.1 Choice of comparators for ERA of GM fish	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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295	Max-Planck-Institut für Evolutionsbiologie	DEU	3.3.2 Choice of comparators for ERA of GM insects	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
296	Max-Planck-Institut für Evolutionsbiologie	DEU	3.3 Choice of comparators	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
297	Max-Planck-Institut für Evolutionsbiologie	DEU	3.4 The use of non-GM surrogates	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
298	Max-Planck-Institut für Evolutionsbiologie	DEU	3.5.1 General Principles	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
299	Max-Planck-Institut für Evolutionsbiologie	DEU	3.5.2 Principles of experimental design	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
300	Max-Planck-Institut für Evolutionsbiologie	DEU	3.5.3 Statistical analysis	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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301	Max-Planck-Institut für Evolutionsbiologie	DEU	3.5.4 Information required	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
302	Max-Planck-Institut für Evolutionsbiologie	DEU	3.5 Experimental design and and statistics	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
303	Max-Planck-Institut für Evolutionsbiologie	DEU	3.6.1 Categories of long-term effects	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
304	Max-Planck-Institut für Evolutionsbiologie	DEU	3.6.2 Guidance to applicants	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
305	Max-Planck-Institut für Evolutionsbiologie	DEU	3.6 Long-term effects	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
306	Max-Planck-Institut für Evolutionsbiologie	DEU	3.7.1 Introduction	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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307	Max-Planck-Institut für Evolutionsbiologie	DEU	3.7.2 Guidance to identify and treat uncertainty	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
308	Max-Planck-Institut für Evolutionsbiologie	DEU	3.7.3 Interplay between ERA conclusions and PMEM	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
309	Max-Planck-Institut für Evolutionsbiologie	DEU	3.7 Uncertainty analysis	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
310	Max-Planck-Institut für Evolutionsbiologie	DEU	3.8.1 Health and welfare aspects for GM mammals and birds	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
311	Max-Planck-Institut für Evolutionsbiologie	DEU	3.8.2 Health and welfare aspects for GM fish	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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312	Max-Planck-Institut für Evolutionsbiologie	DEU	3.8.3 Health and welfare aspects for GM insects	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
313	Max-Planck-Institut für Evolutionsbiologie	DEU	3.8 Aspects of GM animal health and welfare	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
314	Max-Planck-Institut für Evolutionsbiologie	DEU	3. Cross-cutting considerations	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
315	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1.1 Gene transfer and consequences	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
316	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1.2 Horizontal gene transfer	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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317	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1.3 Impacts on biotic components and processes	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
318	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1.4 Pathogens, infections and diseases	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
319	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1.5 Abiotic interactions	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
320	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1.6 Environmental impacts of the specific techniques used for the management of GM fish	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
321	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1.7 Impact on human health	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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322	Max-Planck-Institut für Evolutionsbiologie	DEU	4.1 Specific areas of risk for the ERA of GM fish	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
323	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
324	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.2 Horizontal gene transfer	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
325	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.3 Interactions of the GM insects with target organisms	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
326	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.4 Interactions of the GM insect with non-target organisms	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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327	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
328	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
329	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
330	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.1 Persistence and invasiveness of GM mammals and birds and vertical gene transfer to wild and feral relatives	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
331	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.2 Vertical and horizontal gene transfer	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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332	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.3 Pathogens, infections and diseases	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
333	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.4 Interactions of the GM mammals and birds with target organisms	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
334	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.5 Interactions of the GM mammals and birds with non-target organisms	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
335	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.6 Abiotic interactions	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
336	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.7 Environmental impact of the specific techniques used for the management of GM mammals and birds production systems	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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337	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.8 Impact on non-GM animal health and welfare	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
338	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3.9 Impact on human health	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
339	Max-Planck-Institut für Evolutionsbiologie	DEU	4.3 Specific areas of risk for the ERA of GM mammals and birds	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
340	Max-Planck-Institut für Evolutionsbiologie	DEU	4. Specific areas of risk to be addressed in the ERA	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
341	Max-Planck-Institut für Evolutionsbiologie	DEU	5.1 Case-Specific Monitoring (CSM)	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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342	Max-Planck-Institut für Evolutionsbiologie	DEU	5.2 General Surveillance (GS)	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
343	Max-Planck-Institut für Evolutionsbiologie	DEU	5. Post-Market Environmental Monitoring plan	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
344	Max-Planck-Institut für Evolutionsbiologie	DEU	Assessment	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
345	Max-Planck-Institut für Evolutionsbiologie	DEU	Background as provided by the European Commission and EFSA	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
346	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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347	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
348	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
349	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
350	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
351	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.

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352	Max-Planck-Institut für Evolutionsbiologie	DEU	Summary	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
353	Max-Planck-Institut für Evolutionsbiologie	DEU	Terms of reference as provided by the European Commission and EFSA	Line 2969: Is this just specific to insects or does it also apply to GM fish, birds, mammals? Does to also apply to the regulation of GM plants in the EU? 'The flow of an event from the GM insect into relative species is not an environmental risk in itself;' This is one of the most striking statements in the document and warrants further elaboration.
354	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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355	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.2 Horizontal gene transfer	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
356	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.3 Interactions of the GM insects with target organisms	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release

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357	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.4 Interactions of the GM insect with non-target organisms	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
358	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for

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359	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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360	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
361	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be

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362	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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363	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
364	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be

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365	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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366	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
367	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be

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368	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.2 Horizontal gene transfer	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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369	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.3 Interactions of the GM insects with target organisms	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
370	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.4 Interactions of the GM insect with non-target organisms	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be

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371	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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372	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
373	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be

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374	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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375	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
376	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be

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377	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).

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378	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be continually introduced to the wild population. Once above a certain frequency adaptive genes have the potential to spread away from the release site and could not be recalled by ceasing releases. (III.) Because the males are fertile this will make backcrossing to any wild females in the area frequent, this increases the potential for evolution of resistance to the sterilising transgene by the fertile population. This is because recessive resistance alleles can be much more efficiently selected for in female-killing approaches, compared to a construct resulting in 100% sterility of both sexes (as rarer dominant resistance alleles would probably be required).
379	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	Line 2973 and rest of document: Where are these three probable concerns addressed approaches? In scientific and common usage the term sterile is often understood to be dichotomous, an individual is either sterile or it is fertile. That is unless it is qualified in terms of the degree of sterility e.g. individuals are 40 % sterile (i.e. only 60% fertile progeny are expected compared to a cross between fully fertile parents). Nowhere in the document is the term sterile (used 60 times) clearly defined as being less than 100% sterility. Though for careful expert readers there are implicit acknowledgements that GM sterility may in practice be lower than 100% (lines 3048, 3065 and 3597). However, with the female-killing approach the sterility is intended to have a maximum value of 50% and may be lower if the killing of the daughters is not completely effective for technical and environmental reasons (which has so far proved to be the case). Not only is the fact that the intentional 50% fertility of 'sterile' individuals likely to confuse the reader, but also the ambiguity of terminology makes it unclear if obvious and probable concerns have received no or insignificant attention in the document. (I.) For example, with agricultural pests that develop as larvae and caterpillars on food parts of crops the presence of male larvae is almost inevitable if a fertile pest population exists in the area of release. Consequently, it would be prudent to discuss the need to consider if farming practices and food quality standards are likely to be sufficient to limit human exposure to live or carcases of GM larvae as a rare/'accidental' event. (II.) Because the heterozygous males are fertile, this will make backcrossing to any wild females in the area a frequent occurrence. If the release stock is not of local origin then any adaptive genes (e.g. insecticide resistance alleles most likely unlinked to any transgenic construct) can be

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380	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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381	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.2 Horizontal gene transfer	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm

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382	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.3 Interactions of the GM insects with target organisms	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm

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383	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.4 Interactions of the GM insect with non-target organisms	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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384	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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385	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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386	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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387	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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388	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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389	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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390	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>

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391	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm

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392	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	Line 2937 and rest of document: Where are risk associated with female-killing approaches explicitly addressed? Female-killing techniques (where sons are intended to be fertile) have a particular set of environmental and health concerns that only overlap to a limited extent with dominant lethal techniques that are not sex specific (see second comment to line 2973). However, as far as I can see they are not explicitly considered in the document. Have I missed them? Given that female-killing systems are among the most likely early applications of GM insects (e.g. page 25 Umwelbundesamt-2010, Oxitec Ltd. products OX4139, OX3097D, OX3604C and references 1-4) this is a very surprising omission. Regulatory consideration of a female-killing system has been ongoing since 2011 in the UK (5) and appear to have been endorsed by US regulators (6). Omission of explicit and clear discussion of the female-killing technique in the insect section (but not mammal section) would render the current document much less relevant than it should be. 1 Black, W. C., Alphey, L. & James, A. a Why RIDL is not SIT. Trends in parasitology 27, 362–70 (2011). 2 Gould, F. & Gouldncsuedu, E. F. BROADENING THE APPLICATION OF EVOLUTIONARILY BASED GENETIC PEST MANAGEMENT. 500–510 (2007).doi:10.1111/j.1558-5646.2007.00298.x 3 Gould, F. & Schliekelman, P. Population genetics of autocidal control and strain replacement. Annual review of entomology 49, 193–217 (2004). 4 Fu, G. et al. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences of the United States of America 107, 4550–4 (2010). 5 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 6 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, Docket No. APHIS-2006-0166. Federal Register 21314–21316 (2009).at <http://edocket.access.gpo.gov/2009/E9-10633.htm>
393	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term ‘sterile’ is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term ‘GM induced sterility’ in the insect section is in many places paired with a second term ‘GM sterility or inherited lethality ’ (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term ‘inherited lethality’ is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- ‘Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.’ By this definition it can be guessed that in the GM insect section ‘sterility’ = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and ‘inherited lethality’= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of ‘GM sterility’ appears to correspond to a GM form of the well established term ‘inherited sterility or F1 sterility’ (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term ‘inherited lethality’ appears to correspond to the commonly used ‘dominant

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				lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf
394	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.2 Horizontal gene transfer	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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395	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.3 Interactions of the GM insects with target organisms	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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396	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.4 Interactions of the GM insect with non-target organisms	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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397	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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398	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2.6 Impact on Human Health	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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399	Max-Planck-Institut für Evolutionsbiologie	DEU	4.2 Specific areas of risk for the ERA of GM insects	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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400	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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401	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 2: Hazard characterisation	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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402	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 3: Exposure characterisation	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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403	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 4: Risk characterisation	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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404	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 5: Risk management strategies	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>

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405	Max-Planck-Institut für Evolutionsbiologie	DEU	Step 6: Overall risk evaluation and conclusions	Line 2981 and rest of document: The use of terms relating to sterility must be unambiguously defined in the main text of the insect section and the glossary (this should include explaining their relationship to well established scientific terms). In the insect section of the document the usage of the term 'sterile' is not defined, however based on discussion of the well established non-GM sterile insect technique it is used (at least in some places) to describe the embryonic/larval death of children of the released insects (http://en.wikipedia.org/wiki/Sterile_insect_technique). However, the term 'GM induced sterility' in the insect section is in many places paired with a second term 'GM sterility or inherited lethality ' (lines 1040, 1043, 3047, 3342, 3353, 3596, 3598). The term 'inherited lethality' is not used in the scientific literature in a systematic way to denote any particular technique. Helpfully, this term is defined in the glossary section at the end of the document as:- 'Inherited lethality: gene constructs that when inherited by offspring are fatal to survival.' By this definition it can be guessed that in the GM insect section 'sterility' = the progeny of the released generation are fully viable but infertile as they can have no fertile offspring (?) and 'inherited lethality'= the progeny of the released generation die before sexual maturity (?). But these are only a very unsatisfactory guess. This definition of 'GM sterility' appears to correspond to a GM form of the well established term 'inherited sterility or F1 sterility' (http://en.wikipedia.org/wiki/Inherited_sterility_in_insects). The term 'inherited lethality' appears to correspond to the commonly used 'dominant lethality'. This confusion can most likely be attributed to attempting to generate such a taxonomically and technically broad document. This confusion has important practical consequences (see both comments to line 2937) as many experts will incorrectly assume that the female-killing systems will be covered by the newly introduced term 'inherited lethality'. It would be helpful if regulatory authorities were able to use a similar scientific terminology and avoid introducing novel terms where possible, it really should not be difficult. It is notable that there is almost no overlap in the definitions used here and a related US regulatory document (1). In this document female-killing transgenes are clearly discussed, though unfortunately opting for the ambiguous term 'autocidal'- though at least it is defined in the glossary. 1 USDA-APHIS Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs. Final Environmental Impact Statement. 334 (2008).at <http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf>
406	Max-Planck-Institut für Evolutionsbiologie	DEU	3.3.2 Choice of comparators for ERA of GM insects	Line 1041: Shouldn't SIT and other components of integrated pest management systems also be listed here as examples?

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407	Max-Planck-Institut für Evolutionsbiologie	DEU	2. Strategies for the ERA of GM animals	Line 287 : It would be valuable if there was a explicit commitment by the EFSA to maximise scientific transparency in assessing risks to the environment and human health specific to GM insect techniques where there are limited or no individual opt-outs to exposure. This is a very positive commitment by the EFSA (see also lines 1633, 1556, 1675). However, the regulation of GM insects that are not intended as a food source and are deliberately introduced into wild populations represents a marked departure from what has so far been the remit of the European Food Safety Authority. While EU labelling requirements and global organic standards can be argued to ensure that consumers cannot be coerced into utilising GM plant technologies against their wishes, it more is difficult to see how members of the public and farmers can chose to opt-out of a release of GM insects once it is approved in their local area. This is because:- many GM insects can disperse by flight, away from the area or farm where they were released many agricultural pests develop on the food parts of broad range of crops some flying insects like mosquitoes have females that blood feed on humans. Given this reality and in the context of environmental and human health concerns it might be valuable to explicitly restate the policy of the EFSA that:- 'The balance between transparency and confidentiality rules is determined by the approach that the maximum amount of information linked to EFSA's activities is to be disclosed or made accessible to the public and that only the essential minimum shall be kept confidential.'(1) It is difficult to underestimate the positive role that the EFSA could play in facilitating the generation of a high quality scientific consensus in a transparent manner. 1 EFSA TRANSPARENCY IN RISK ASSESSMENT CARRIED OUT BY EFSA. 2002, 1–16 (2006).E405
408	Max-Planck-Institut für Evolutionsbiologie	DEU	Summary	Line35-36: It is a very positive commitment by the EFSA that they will, where necessary, proactively generate scientific data if this can readily address significant voids on questions of environmental and human health (assuming the voids can realistically be experimentally addressed). However in the absence of a concerted effort to secure access to relevant living biological material without onerous restrictions for independent researchers it is conceivable that even the EFSA would suffer the same restrictions that have limited the unbiased study of commercialized GM crops (1). 26 Anonymous Scientists' (2008) Comment to FIFRA Scientific Advisory Panel DOCKET EPA-HQ-OPP-2008-0836-0043. 1. Available: http://www.regulations.gov/ - !documentDetail;D=EPA-HQ-OPP-2008-0836-0043

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409	Max-Planck-Institut für Evolutionsbiologie	DEU	Abstract	line 17: Terms used in this extremely broad document must be defined and used consistently. The consideration in a single document of an enormous range of potential genetic modifications across an enormous taxonomic range is a very ambitious undertaking. Almost inevitably this risks inconsistent application of terminology in different parts of the document. One example of this is the use of the word 'sterile'. This word has a common usage, understanding, that sterile individuals are incapable of generating live young when mated with an individual of the same species. This is in fact how the term is used in reference to sterility in fish through induced polyploidy (line1068). The common definition of sterile is often extended by scientists to also describe individuals as sterile if all their progeny are viable but never fertile (i.e. they are capable of fertilisation but their children either die prior to sexual maturity or they never sexually mature). Given the importance of this word and the obvious potential for confusion is it remarkable that nowhere is the term defined, even for specialists the way it is used has to be guessed in each section. In the bird and mammal section, 'sterile' is used to describe a situation where daughters of released male GM rabbits are completely infertile but the sons are fertile (line 4402). Consequently, the released 'sterile' GM male rabbits will have a normal number of offspring but the daughters will be infertile. While, it is correct to call this a sterility based population strategy, in the absence of a proper explanation the common understanding of sterile will be misleading as the released sterile males have a normal number of offspring. The dominant (near universal) scientific term for this strategy is 'female-killing', however this is not used anywhere in the document (see comment to line 2937 and references). In the insect section of the document, sterile is not defined and its use can only be guessed at, even by experts (see comment to line 2981). It is difficult to be sure, but it appears that the term 'sterile' or the newly introduced term 'inherited lethality' singly or jointly used to describe techniques where a normal number of offspring are born, 50% of which are fully fertile (the sons). Misleading and inconsistent terminology should be resolved as a priority, not only to assist readers, but also as a means to resolve the practical scientific problems it creates (see comment to line 2937).

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410	Max-Planck-Institut für Evolutionsbiologie	DEU	Abstract	Line 14: The GM insect sections should be strengthened to ensure that areas of obvious public concern shall be considered in a scientifically rigorous and transparent manner even where probability of exposure can be reasonably argued to be low. GM moths (USA) and mosquitoes (Cayman Islands, Malaysia & Brazil) have already been released in open field trials and UK regulators initiated the consideration of the release of a GM moth in 2011(1). All of these events have attracted national and international press coverage and it can already be predicted with confidence what public concern is likely to be focused on in the future:- (I.) Concerns about human health impact of ingestion of GM insects as eggs, larvae, and adults (II.) Concerns about human health impact of being bitten by GM mosquitoes (see comment to line 4242 and 4249) (III.) Concerns about unintended ecological effects It should be made clear in this document that ERAs will address all these concerns. Strikingly point II. is totally omitted from the document, though it has been widely discussed in the media and in the draft document (pages 97-98, 135 Umweltbundesamt 2010, see also comments to lines 4242 and 4249). While point I. is covered in the document, it is far from clear what if any scientific information will be considered if the applicant argues that public exposure will be minimal or limited to the purely accidental. In any application to release a GM insect which can develop on food crops it will, in my opinion, prove insufficient to solely point out the ways in which farming practices and application of food standards regulations will restrict public exposure. This will only have a limited impact on public acceptance, as many members of the public will know from their own experience that they do encounter insect larvae in their fresh food. Even if exposure can be reasonably argued to be minimal, it is short sighted not to fully discuss the hazard in an appropriate scientific document. This is particularly true with respects to points I. and II. as the simplicity of many of the experiments required would not impose a burden on applicants. For example, in a scientific document considering the release of a GM moth expressing only the fluorescent protein dsRED, even if exposure risk is minimal it must be clearly explained why its ingestion at any life stage is not likely to pose a significant human health risk (including an experimental assay for digestive enzymatic degradation of dsRED, section 3.3 (2)). ERA documents should clearly explain the reasoning behind conclusions, the scientific evidence they are based on and which scientists were involved. This document should be made publically available prior to regulatory approval, along with all scientific evidence relating to environmental and human health concerns. Clear discussion of these concerns should be seen as a commitment to resolve all realistic concerns in an appropriate scientific forum and not necessarily viewed by anybody as a legitimisation of their scientific basis. Combined with early EFSA involvement in experimental field trial regulation (see comment to line 8) this provides the most viable route to the timely application of safe techniques that could offer real value relative to currently available insect control techniques (e.g. in terms of reduced use of insecticides, increased sustainability etc). 1 ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011).at http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf 2 Assessment of foods derived from recombinant-DNA plants. CAC/GL 45-2003 45, 18 (2003) http://www.codexalimentarius.org/standards/list-of-standards/en/

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411	Max-Planck-Institut für Evolutionsbiologie	DEU	Abstract	Line 8: It is critically important that the use of the term 'market' is clearly defined, as this is likely to dictate the future practical importance of the document. Does this document cover applications for non-commercial experimental releases of GM animals in the EU regardless of their scale or duration? If not why not? If this document covers only approval for release of GM animals as a product within the EU (defined as something sold or licensed for a monetary fee) then this document is very likely to be rapidly superseded by the regulatory decisions made during the experimental field trial stage (these must occur prior to applications for commercial approval, see section 3 of document). With respect to the approaches involving the intentional releases of animals into wild populations, if all field trials regardless of their scale or containment will be solely the responsibility of member state national regulators, then it is almost inevitable that the first releases in the EU will be in a regulation friendly member state(s), potentially with a limited statutory mandate for transparency and be conducted as a 'free offer' (alternatively all field trials will be conducted outside of the EU, possibly in bordering states). In these circumstances this EFSA document would have little practical significance. If however 'commercial' and 'market' are defined as in Directive 2001/18/EC as 'placing on the market means making available to third parties, whether in return for payment or free of charge' part A article 2(4) and 'Placing on the market also covers import.' article 1, then this document is much more likely to be of broad practical significance. This would enable the EFSA to play a proactive role in coordinating the scientific evaluation of these novel techniques and ensuring the transparency of this process from the earliest stage*. This would be of particular value for the techniques that involve the deliberate release of into wild populations GM organisms which have the capacity to move across borders e.g. flight by adult GM insects or unintentionally transported as larvae. Consideration of such techniques at the EU level offers the best opportunity to ensure that avoidable uncertainty does not disrupt trade or needlessly cause public concern. Asserting such a role speaks to many of the reasons for the very existence of the EU in the minds of its citizens, and could permit more rapid development of this potentially valuable technology Line 248-252 appears to indicate that a very narrow definition of 'market' will be used, removing the obligation for the generation of publically available scientific opinions of the EFSA in the experimental field trial stage. It is stated that the document 'excludes their release for experimental purposes under Part B 250 of Directive 2001/18/EC (EC, 2001).' at the very least the article and reason for this short-sighted exclusion should be given. It should also be clarified if imports of experimental material from outside the EU will also be excluded from EFSA consideration (also possible under part B of Directive 2001/18/EC). *It is noteworthy the UK regulators (and potentially other member states) are already in the process of considering experimental releases of a genetically modified diamond back moth. ACRE Acre/11/m4 advisory committee on releases to the environmental minutes of the 134 meeting of ACRE (UK). 1–9 (2011). at http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf
412	MPI - Evolutionary Biology	DEU	4.2.4 Interactions of the GM insect with non-target organisms	It is difficult to know where to include comments on farming certifications within this framework but given the size of the organic farming industry this document should probably specifically deal with potential impact of GM insect releases on farms certified as organic. Asking the question 'Could a release potentially impact the certification of organically produced produce?'.
413	MPI - Evolutionary Biology	DEU	4.2 Specific areas of risk for the ERA of GM insects	Any document of this nature is always going to tend towards generality due to the need to anticipate future developments but given the advanced state of the GM insect field, when compared with that of fish (section 4.1), mammals or birds (section 4.3), it seems odd that this section did not cover more of the existing literature. The use of case studies in section 4.3 provides an excellent way to identify potential aspects that would need addressing for appropriate regulation. I am also unsure as to how a document examining GM insects cannot discuss in detail the open releases of the partially sterile Oxi513a Aedes aegypti mosquito in Malaysia, Cayman Islands and Brazil. The EFSA is fortunate in that it is able to take advantage of work already conducted in these countries, and others, regarding the release of GM insects. It is possible to carefully examine the regulatory documents and build on their already established frameworks. To not do so would be to lose many of the advantages in delaying the deployment of GM insect technologies. It would be my recommendation that the GM insect section be redrafted to move it away from a more speculative section to a section focused on existing GM insect technologies. Potentially using the both the sterile insect systems discussed in either Harris et al. (Nat Biotechnol. 2011 Oct

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				30;29(11):1034-7.) or Horn and Wimmer (Nat Biotechnol. 2003 Jan;21(1):64-70), the flightless system discussed in Fu et al. (Proc Natl Acad Sci U S A. 2010 Mar 9;107(10):4550-4.) and any of the fluorescence insects as case studies in much the same way as section 4.3. Following this recommendation the section could address the issues identified in 4.2.1-4.2.6 on a case-by-case approach, although mentioning, as done already in this document, that these are merely meant as a guide not an exhaustive analysis.
414	Netherlands Commission on Genetic Modification (COGEM)	NLD	Terms of reference as provided by the European Commission and EFSA	The size of the document, the relative short period available for reviewing, and the fact that the public consultation period overlaps completely with the summer holidays, hamper a thorough and detailed assessment of the draft guidance. Therefore, in its comments the Netherlands Commission on Genetic Modification (COGEM) is forced to restrict itself to main issues without going into details. GM animals are a highly controversial subject in Europe, especially due to moral objections. Although the document focuses on the ERA of GM animals and ethical and socio-economic issues are not part of the scope of the document, COGEM points out that the unfortunate timing of the public consultation does not help to gain public support. The overlap with the summer holidays limits the possibility of stakeholders and interested parties to submit comments and thus fuels public distrust.
415	Netherlands Commission on Genetic Modification (COGEM)	NLD	Assessment	The EFSA draft guidance is an impressive and lengthy document, which seems to cover nearly every conceivable aspect of the ERA of GM animals. As such, it is of considerable value for both applicants and risk assessors. The document provides a very useful enumeration of points-to-consider for the ERA of GM animals. However, the document fails in its intention to provide detailed guidance for applicants. It lacks in identifying clear criteria or methods for the ERA, much of the text is ambiguous, and all the aspects and elements that presumably have to be considered in the ERA of GM animals are dealt with in the same manner, irrespectively of their relative importance for the ERA. For instance in paragraph 4.2.3 (Interactions of the GM insects with NTOs) it is stated that changes to other ecosystem functions such as decomposition of organic matter or water regulation have to be considered. The possibility that such changes occur are far-fetched and the ERA should focus on changes in competitiveness, displacement of insects by the GM insect, and changes in aggressive behaviour. Strikingly, in the paragraphs 4.2.1 (Persistence and invasiveness, including vertical gene transfer) and 4.2.6 (Impact on human health) little attention is given to possible changes in behaviour of the GM insect, especially those which are important in the interaction with humans, like raised aggression or adaptation to live indoor houses or outdoors. Some of the elements of the ERA mentioned seem too far-fetched or not related to the genetic modification. On page 82 of paragraph 4.2.3 (Interactions of the GM insects with NTOs) it is stated that a successful GM based suppression program can lead to complacency about environmental hygiene for mosquito control, making the impact of any failure in a GM insect campaign more serious than it may have been. Although this is probably true, it is a problem associated with every successful prevention, eradication or suppression program and not associated with genetic modification. In all three chapters on the ERA of GM fish, insects, and mammals and birds considerable attention is given tot horizontal gene transfer. As indicated in the different paragraphs of the guidance document horizontal gene transfer is a rare event. Horizontal gene transfer possibly only occurs between organisms, which are in close contact like symbionts and their host, or parasites, and on an evolutionary time scale. The element of the need for ‘intimate contact’ between organisms is lacking in the paragraphs on horizontal gene transfer. On page 8 it is mentioned that the guidance document covers (1) captive, (2) semi-captive and (3) non-captive GM animals. The differences between these three groups of animals are of considerable importance for the ERA. However, this distinction appears to play no role in the deliberations on the ERA in the guidance document. At least the consequences for the ERA of the various degrees of captivity should be discussed in the chapter on cross-cutting considerations. Finally, there appear to be differences in the set-up of the chapter on GM mammals and the chapters on GM fish and insects. Such textual differences can lead to confusion. Editing and shortening of the text and removal of ambiguities would further improve the usefulness of the document.

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416	Center for Food Safety	USA	3.1.3 Selection of the relevant receiving environments	The recieving environment should be carefully reviewed to exclude any environment where an endangered wild relative of the GMO animal lived at anytime in recent history. This is especially true for the endangered Atlantic salmon as populutions that have disappeared from various watersheds for years are now being restored and breeding wild populations are again being found in places they were thought for years to be extinct or nearly extinct. Geographical isolation of the GMO animals from their wild relatives or domesticated relatives that they are likely to breed with should be a major criteria for selection of the receiving environment. It should be assumed that the animals will at some time escape. Physical containment will not prove by itself to be adequate unless coupled with geographic isolation, too.
417	Center for Food Safety	USA	2.2 Information to identify potential unintended effects	Given that many of the genetically engineered animals have morphological changes that may make them more prone to become ill, the assessment should include a complete review of the amount and kinds of antibiotics given to the animals as part of the review of "unintended" consequences.
418	Center for Food Safety	USA	2.1.5 Step 5: Risk management strategies	Risk mitigation strategies must include labeling of the genetically engineered organism for the initial purchaser of the organism or they will not be able to implement appropriate environmental mitigation strategies. On page 6, line 186, the document says that the "EFSA GMO panel will not consider issues related to risk management (e.g. tracebility, labelling, conexistence." However, an applicant may not be able to adequately address some of the problems without having some plans related to tracebility, including labeling. If a risk is related to consumption of a food derived from a GMO, then a labeling tool is a responsible scientific step if a recall were later needed. It is not a scientific step to take the tools of tracebility or labeling off the table as a risk management strategy even before the risk has been characterized.
419	Center for Food Safety	USA	2.1.4 Step 4: Risk characterisation	Again, all data used to make a risk characterization should be available to the public after the risk has been characterized. This should especially include any health, safety, and environmental risk data. These cannot be held back as being "confidential".
420	Center for Food Safety	USA	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	This section permits the use of unpublished research data to help with hazard identification. However, after the hazard has been identified publication of all of the data used to make this decision should be required.
421	Belgian Biosafety Advisory Council	BEL	Glossary	Page 173: Outbreak is also often use to characterized a sudden growth of a pest population that exceed the economic threshold. The definition given in the glossary is more that of invasive species.
422	Belgian Biosafety Advisory Council	BEL	References	Page 169, reference Umweltbundesamt, 2010: The link on the document is not correct.
423	Belgian Biosafety Advisory Council	BEL	4.3.5 Interactions of the GM mammals and birds with non-target organisms	- Page 133, line 5695: Biomass is not always a pertinent criteria, for example, rare species often represent a small relative biomass of an ecosystem, at least it should be weighted by abundance and size. I think that this criteria should be better linked with species vulnerability and could be replaced by its functional role in the ecosystems, notably in the case of key species in the ecological network. This point is quite different that the ecological services it gives, as ecological function may stress the importance of the species in the present state of the ecosystems. Therefore we should omit lines 5695-5697. - Page 138, table 7: I wonder if effect on Predator 2 via top predator should not be positive instead of negative. One can suppose that the presence of the GM animal releases the pressure of the top predator on predator 2. - Page 138, line 5836: "…listed in Table 7... " instead of "...listed in Table 2..." - Page 136, line 5776: This line should refer to Table 7 instead of Table 2. - Page 138, line 5823: This line should refer to Table 7 instead of Table 1.

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424	Belgian Biosafety Advisory Council	BEL	4.3.4 Interactions of the GM mammals and birds with target organisms	- Lines 5402-5405: We have questions on the focus of the problem formulation, which is as stated in the EFSA ERA GD “to determine the likelihood that the TO will evolve mechanisms to reduce the efficacy of the modification,…”. To our opinion, the focus should be on the environmental concerns (protection goals) for TO. Information on the likelihood that efficacy is reduced, can inform the assessment of those environmental concerns. We propose to rephrase the focus of the problem formulation. - Lines 5408-5422: We can see that an increased virulence of pathogen strains, can lead to an increased risk for GM animals. However, when it comes to explaining how these pathogen strains (with increased virulence) can lead to increased risk to the environment, the text needs to be nuanced. While an increased virulence will have an effect on the GM animal (it is more vulnerable), the effect on the environment is less straightforward. We postulate that – taken the case-study of the avian flu resistant chicken into account – current medication practices would still be applicable in case of increased virulent pathogens. Hence, in such case, there would be no additional environmental risk. Opposed to describing first the worst-case scenarios (use of larger doses of medication or alternative medication), we suggest that it is first clarified that only in the case current medication practices will be no longer sufficient, applicants should address the risk to the environment according to the guidance notes in this section. - Page 128 line 5479: The opening bracket is missing.
425	Belgian Biosafety Advisory Council	BEL	4.3.3 Pathogens, infections and diseases	- Page 119, line 5067: "...in the context…" instead of "...in the contest…". - Page 125, line 5346: The term "biosecurity" is not correct in this context ; it should be replaced by "biosafety". Whereas biosafety aims at protecting public health and environment from accidental exposure to GMOs and/or pathogens, biosecurity deals with the prevention of misuse through loss, theft, diversion or intentional release of pathogens, toxins and any other biological materials. - Page 123, line 5260: “hazard characterization of the hazard”: omit “of the hazard”. - Page 122, line 5216: This line should refer to section 4.3.3 instead of 4.3.1.
426	Belgian Biosafety Advisory Council	BEL	4.3.2 Vertical and horizontal gene transfer	- Page 114, line 4822: Use the word “breed” instead of species here (cfr Frankham). - Page 115, line 4908: Semi-colons should be placed between the references instead of colons. - Page 115-118: Horizontal gene transfer in mammals and birds: not documented to my knowledge: should 3 pages be devoted to this hypothetical event? All references given are made to lower eukaryotes, not vertebrates
427	Belgian Biosafety Advisory Council	BEL	4.3.1 Persistence and invasiveness of GM mammals and birds and vertical gene transfer to wild and feral relatives	- Page 107, line 4512: Question 1 should be in bold and not underlined. - Page 110, lines 4637-8: This sentence is hardly understandable in its current wording => Omit lines 4637-4638: taking the biological definition of commensalisms it means all domestic animals for meat, milk and eggs can be seen as global invasive pests.
428	Belgian Biosafety Advisory Council	BEL	4.3 Specific areas of risk for the ERA of GM mammals and birds	Page 104, line 4413: This line should refer to Table 5 instead of Table 1. This is also true on page 105, line 4423.
429	Belgian Biosafety Advisory Council	BEL	4.2.4 Interactions of the GM insect with non-target organisms	Page 88-89, line 3684: In step 1, a point is lacking. It is essential to take also into account "A change in apparent competition with beneficial insect or apparent mutualism with pest insect and the ecological function they provide" (see Abrams et al. 1988, Ecology Vol. 79, No. 1 (Jan., 1998), pp. 201-212, and van Veen et al. Apparent competition, quantitative food webs, and the structure of phytophagous insect communities, Annual Review of Entomology, Vol. 51: 187 -208).

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430	Belgian Biosafety Advisory Council	BEL	4.2.3 Interactions of the GM insects with target organisms	- Page 83, line 3434: In all that section, the risk of the inactivation of the modified gene in the GM population should also be considered and evaluated with its consequences. - Page 85, step 3, line 3539: Mating strategy characterization should include polyandry or polygyny, male precedence and spermatic competition. Attention should be drawn to parthenogenitic population and existence of thelytokous strain linked to Wolbachia or not. The term thelytokous should also be explained: fertile eggs are males and infertile eggs become females!!
431	Belgian Biosafety Advisory Council	BEL	4.2.1 Persistence and invasiveness, including vertical gene transfer	- Page 75, 3081: Characterization of fitness changes is not enough, trait changes should also be considered. For instance, a heat resistance trait does not necessarily change the fitness but may change the possible distribution of the species. In consequence, we propose to change the sentence like this “The offspring will express fitness or traits changes”. Criteria to be measured to evaluate fitness change are not described, see the general comments.
432	Belgian Biosafety Advisory Council	BEL	4.1.6 Environmental impacts of the specific techniques used for the management of GM fish	- Lines 2698-2701: We do not understand the meaning of this sentence. Can this be rephrased? - We consider lines 2701-2703 out of scope of this section. Measures to prevent escape and assessment of the efficacy of these measures should be addressed in section 4.1.1 on Gene transfer and consequences. - Line 2743: What is meant with “accessible ecosystems as a whole”? Is this the receiving environment?
433	Belgian Biosafety Advisory Council	BEL	4.1.5 Abiotic interactions	The issues addressed in the introduction of this section belong to our opinion rather to the problem formulation phase, while the issues addressed under step 1 we consider more as an introduction to the specific area of risk. We therefore propose to move text in the appropriate section. Further, we ask EFSA to reformulate the environmental concerns. We do not consider “an altered tolerance to abiotic factors” as an environmental concern. To what negative environmental impacts can these alternations lead? A clear formulation of the concern is necessary in order to be able to comment on further steps.
434	Belgian Biosafety Advisory Council	BEL	4.1.4 Pathogens, infections and diseases	- We consider a lot of the information in this section as ‘nice to know’ information and not as ‘need to know’ to conduct an ERA of GM fish. In line with our general comment to focus guidance more, we suggest to concise the introduction of this section. - Lines 2466-2468: The key question of the problem formulation is formulated as “might the GM fish differently influence pathogens in the environment in comparison to its comparator”. We suggest clarifying what is meant with ‘influence’. Does ‘influence’ refer to abundance or pathogenicity or something else? Further, it is not clear what the main concern is about. Is this pathogenicity, fish health or development of disease resistance (which is addressed in step 2)? We propose to formulate the key question (concern) more clearly. A clear formulation of the concern is necessary in order to be able to comment on further steps.
435	Belgian Biosafety Advisory Council	BEL	4.1.3 Impacts on biotic components and processes	- Lines 2257-2303: The description of environmental concerns related to the GM fish with the environment is to our opinion part of the problem formulation and not of hazard characterisation. We therefore propose to address the concerns (e.g. decrease of abundance of native species) under problem formulation. - Line 2258: states that “Applicants should examine whether the GM fish has changed foraging behavior…”. Can it be clarified if this is a standard requirement for all GM fish? We would argue this information is needed on a case-by-case basis depending on the trait considered. - Lines 2297-2303: As stated, impacts on health are addressed in another section. We thus suggest deleting this §. See also general comment to focus guidance more. - Lines 2332-2342: In step 4 risks need to be characterised. We therefore disagree with the wording of this section, where applicants are requested “to consider” receiving environments, interactions etc. In this stage conclusions need to be drawn on the risk of any harmful characteristic identified during problem formulation. We propose adapting the text.

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436	Belgian Biosafety Advisory Council	BEL	4.1.3 Impacts on biotic components and processes	- Line 2220: Target and non-target effects are not defined in Directive 2001/18/EC. Target and non-target organisms on the other hand are. So please rephrase this sentence. While target organisms are defined in the GD, non-target organisms are not. We think it would be better to define both. - Line 2230: “predation, competition, habitat alternation, inter- and intraspecific hybridization” are not examples of direct effects, but processes which could lead to adverse direct effects. We propose to delete them. The examples in lines 2235-2237 on the other hand are examples of direct effects and not - as stated in the GD - “consequences of direct effects”. We suggest correcting the text. - Line 2240: We are not in favour of using the term ‘focal species’ here as it has another meaning than the one proposed in the section Four steps for selecting focal NTOs (starting at line 5641) and EFSA’s GD on assessment of impacts on GM plants on NTOs. Further, as the term is not used further in the section on GM fish, we question the relevance of introducing this term. We therefore suggest to omit lines 2240-2242
437	Belgian Biosafety Advisory Council	BEL	4.1.1 Gene transfer and consequences	- Page 47, line 1881: "…the presence of a recombinant DNA…" instead of "…the presence of an recombinant DNA…" - Line 1876: As stated this section solely “focuses on genetic and population effects of the GM fish and any other recipients” (lines 1871-1873). Can it be clarified in the first § of section 4.1.1 what is meant with ‘population effects’. Are these effects on fish populations, or more general effects on any population of flora and fauna? Some more detailed explanation would add clarity to the text. When reading further, we understand that both effects on fish populations and effects on flora and other fauna than fish are covered in section 4.1.1. However, the latter aspect (effects on flora and fauna) are also covered in section 4.1.3 and as stated in line 1871 are out of scope of section 4.1.1. Hence we do not understand why this aspect is further addressed. We therefore propose to focus on the issues one wants to cover in this particular section and to delete § 1875-1878 & lines 1913-1917 dealing with biotic interaction issues. - Line 1894: Concerning “the spread of fish diseases during import, transportation, storage, handling and processing” we consider this as an important issue. However, if comparative analysis does not indicate differences in the presence of fish diseases, we do not consider this issue should be further addressed in the ERA of GM animals. In this particular case, existing regulations e.g. on hygiene for food of animal origin (Regulation (EC) No 853/2004) should apply. We therefore, propose to delete “the spread of fish diseases” from this section and to explain more up front that existing regulations will still apply to cover certain issues. - Lines 1938-1939: As in line 364, a hazard has been defined as an adverse effect. Hence it is odd to say that “any hazard (or adverse effect) … might lead to adverse effects”. We therefore propose to change the sentence into “any hazard … might lead to harm”. - Line 2064: Overall risk evaluation and conclusions: We disagree that the conclusions on the overall risk should be on ‘extents’. This should be on assessed impacts or harm!
438	Belgian Biosafety Advisory Council	BEL	4.1 Specific areas of risk for the ERA of GM fish	It is said that the GD covers both commercial release and any associated unintended or accidental release of GM animals into the environment. However, from the GD it is not clear if data requirements requested in sections 4.1.1 to 4.1.7 apply in both cases. The GD could be clearer on this point.

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439	Belgian Biosafety Advisory Council	BEL	4. Specific areas of risk to be addressed in the ERA	- Overview page 46: We do not understand why and how impact on biogeochemical process is addressed in the interaction with non target-organisms? It is not clearly specified. - Page 46, figure 5: The colour code makes the figure difficult to read when printed in grayscale. - Figure 5: In the text it is explained that the terminology for specific areas of risk is changed when deemed necessary. However, when it comes to the first area of risk (gene transfer or persistence and invasiveness) we do not understand why 'gene transfer and consequences' is used in case of GM fish and 'persistence and invasiveness' in case of GM insects, mammals and birds. As for GM fish also persistence and invasiveness are addressed in the text (see e.g. line 1866), we consider also persistence and invasiveness could be used as title of section 4.1.1. We are of the opinion that harmonising the terminology used will lead to clearer guidance. - Further it is explained that the GM fish section 4.1.3 covers both interactions with target and non-target organisms. However, when reading section 4.1.3 we would argue that this section only deals with interactions with non-target organisms. We do not understand the reasoning given by EFSA and would propose to stick to the common terminology (interactions with target and non-target organisms) as this will add clarity to the GD.
440	Belgian Biosafety Advisory Council	BEL	3.8.1 Health and welfare aspects for GM mammals and birds	Line 1771: Omit "for non-food and –feed animals"; also for food and feed animals a comparator group may not be the best yardstick as the genetic load already carried by the non-GM line itself may be considerable; in the text examples are given for non-food animals (brachycephalic dogs), but also examples can be given for food animals (chonrodisplasya chickens etc.)
441	Belgian Biosafety Advisory Council	BEL	3.7 Uncertainty analysis	Compared to the ERA GD on GM plants the topic of uncertainty analysis is more elaborated. Does this imply that other criteria apply for GM animals compared to GM plants?
442	Belgian Biosafety Advisory Council	BEL	3.5.1 General Principles	Page 31, lines 1150 to 1158: We have trouble with this paragraph. First, Heard et al., 2003 is not in the list of references. If the correct reference is "Heard et al, Phil. Trans. R. Soc. Lond. B 2003 358, 1819-1832, doi: 10.1098/rstb.2003.1402", it does not seem appropriate in this paragraph. What is explained in the Guidance Document does not seem to come from this article. We also do not understand what is meant by "Multiplicative effect size" in this context. We think this concept is very poorly explained here, not deep enough and could lead to confusion on the choice of confidence intervals. We think this whole paragraph should be rewritten more explicitly including the need for clarification in what sense is the multiplicative effect, We suppose in a sense that we take more security compared to the results observed. We wonder whether this paragraph should not be deleted, at least in this form.
443	Belgian Biosafety Advisory Council	BEL	3.4 The use of non-GM surrogates	- Line 1086: "…that can be related to the specific to the GM animal under consideration": This sentence is not clear. Probably a word missing after specific. - Although we can agree that non-GM surrogates could be particularly useful as a source of historic or parallel data to inform risk assessment, we do not agree with the idea to deliberately release in nature non-GM surrogates with similar characteristics or traits to those of the GM animals being considered to obtain de novo data. From a legal point of view, it is true that releasing such non-GM surrogate would not be prohibited, nor subject to a preliminary risk assessment. However, from a scientific point of view, it is not acceptable to gather environmental data by the introduction without any ERA of a non-GM animal which might have negative ecological impact. This would be also in contradiction with the reasoning developed in lines 904-924. - This chapter describes the use of non-GM surrogates in the ERA of GM animals as a source of historic data. Information on non-GM (plant) surrogates can also inform the ERA on GM plants. In the ERA GD on GM plants this issue has been referred to by using terms such as historical knowledge/data and baseline data. Referring to these historical knowledge/data now in terms of 'use of non-GM surrogates' in this GD only creates confusion (as if something new needs to be considered). We therefore suggest (1) to also use the wording historical knowledge/data and baseline data in the GD on GM animals and (2) to only use the term non-GM surrogates when one wants to obtain de novo data without using the GM animal. - Further we note that when it comes to GM plants the use of non-GM surrogates to obtain de novo data is not mentioned in the ERA GD on GM plants (e.g. a HT plant obtained through mutation breeding could serve as a surrogate). We understood that studies with the GM plant where considered necessary by EFSA to cover unintended unanticipated effects. How does the non-GM surrogate approach match with the approach taken for GM plants? We also wonder when such de novo data would be useful. As stated in the text (line 1093-1094) "the use of surrogates may be advantageous

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				because their impacts are already well documented". If they are well documented, why would one conduct a de novo experiment with a non-GM surrogate? Could an example be given? If impacts are not well-document for the non-GM surrogate, we postulate a non-GM surrogate experiment could cause as much harm to the environment as a GM experiment. What would be the minimum criteria a non-GM surrogate needs to apply to, before it can be used in an experiment?
444	Belgian Biosafety Advisory Council	BEL	3.3.2 Choice of comparators for ERA of GM insects	- Page 28, Line 1033 to 1036: The text states that the comparator should be the non-GM insect with a close genetic background, with which we agree but it proposes also comparison with alternative management scenario like insecticides. This is very different approach aiming at comparing the impact of the insecticide use on the environment with that of the use of the GM insect. We feel that the text should be clarified by clearly distinguishing between (i) comparators for ERA of GM insects, and (ii) comparators for ERA of management systems using GM insects. - Line 1034: Please note that not the applications are genetically modified, but the animals. Therefore, the term GM application (and also GM sterile, GM replacement and GM pollinators) is incorrect.
445	Belgian Biosafety Advisory Council	BEL	3.3.1 Choice of comparators for ERA of GM fish	Line 991: Taken the definition of the accessible ecosystem into account, are 'an escape zone' and 'an accessible ecosystem' two terms referring to the same zone? Or should we rather consider the escape zone as a part of the accessible ecosystem and write it as "in possible escape zones of the accessible ecosystems"?
446	Belgian Biosafety Advisory Council	BEL	3.2 Experimental environment	- Lines 804-813: Concerning the reasoning on the relevance of the tiered eco-toxicological approach in the assessment of pesticides, impacts of GM plants and GM animals, we want to note that we disagree with the statement that the tiered approach is widened for the RA of GM plants. It is not the tiered approach that is widened, but the RA itself (with more focus on unintended effects). We therefore propose to delete lines 804-808. Further it is stated that "the tiered approach has less relevance for the ERA of GM animals". We would propose to be careful with such general statements, especially because there is little practical experience with the evaluation of risks due to the release of GM animals. Moreover, we postulate that depending on the GM animal (and trait) considered the tiered approach may be a valuable tool in assessing effects on NTOs and thus have as much relevance when assessing a certain GM plant. - Lines 825-834: For any trial conducted with a GMO, one needs to consider whether containment measures are needed. The consideration and evaluation of these containment measures fall under the scope of Part B applications and thus fall out of the scope of this GD which does not cover issues for experimental purposes. We therefore suggest deleting this paragraph.
447	Belgian Biosafety Advisory Council	BEL	3.1.3 Selection of the relevant receiving environments	Line 737: NTO? : first time this abbreviation is used in the text. So the full wording should be included here (Non-Target Organism).
448	Belgian Biosafety Advisory Council	BEL	3.1.2 Identification and characterization of the receiving environments	- Page 21, line 713, point (2): Add endosymbionts: pest, pathogens and endosymbionts associated with GM animals. - Page 21, table 2: The colour code makes the table difficult to read when printed in grayscale. Suggestion : put the « abiotic » factors in italic. - Line 667: What is meant with "receiving environment to which the GM animal and its by-products have access"? Does 'have access' refer to 'will be released' or to 'will be released, can escape to or be distributed to' (as in the definition of receiving environment)? Can this be clarified? Further, we want to note that it is not always clear to us why sometimes the term 'receiving environments' is used in the GD, while sometimes the term 'accessible ecosystems'. The terms seem to be interchangeable with no difference in meaning. - Line 680: Please note that not the traits are genetically modified, but the animals. Therefore, the term GM trait is incorrect. - Line 713: Again in line with the comment on line 397, we ask EFSA to clarify which by-products would be important to consider in the ERA of GM animals. Further the terms, faeces and urine fall under the term 'excreta' and could be omitted; the term waste material we consider too vague. - Line 714: Does the word 'products' also refer to 'by-products' or are other products considered here? Can this be clarified?

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449	Belgian Biosafety Advisory Council	BEL	2.2 Information to identify potential unintended effects	- Line 580: Can it be explained what is meant with “targeted” compositional analysis? In the GMFF GD of GM animals one speaks of ‘compositional analysis’. Is there a difference between the ‘targeted compositional analysis’ described in the ERA GD and the ‘compositional analysis’ described in the GMFF GD? - Lines 589-592: we note that this is a new requirement compared to the GD on RA of FF from GM animals and absolutely no guidance is given on how to obtain these data. Guidance should be given on how to obtain these data as for the interactions between the GM animal and its receiving environments
450	Belgian Biosafety Advisory Council	BEL	2.1.5 Step 5: Risk management strategies	Lines 543-551: To our opinion this § (on proposal of risk management strategies) belongs to step 5.
451	Belgian Biosafety Advisory Council	BEL	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	- Line 364: We propose to delete “harm to or” as to our understanding, ‘harm’ cannot be considered as a ‘hazard’ (line 364 states that harm or adverse effects are alternative terms for hazard). Hazard is often used as an alternative word for adverse effect, but has clearly a different meaning than harm (namely a hazard could lead to harm, but not necessarily). - Line 364: Only human health is considered here and not animal health. We consider ‘animal health’ should be included to be in line with line 10. - Line 382: We propose to delete the word ‘qualitative’ as the term ‘qualitative exposure’ is only used once in the whole GD (namely in line 382); the term ‘quantitative exposure’ is not used in the GD; it is not a common term used in RA of GMOs; and ‘qualitative’ does not add to the explanation of what type of exposure is considered here. This is well-explained in the brackets (identification of exposure pathways). - Lines 386 & 392: Could it be better explained what is meant with ‘the release of the live animal into the environment’. We understand that for example if a GM chicken is held as a captive GM animal indoors for egg production, this would be considered as a release into the environment, with the receiving environment being a stall (case 1 – lines 386-391). If this GM chicken is transported to a slaughter house, we understand this would not be seen as a release into the environment (case 2 – lines 392-398)? However, according to the definition of receiving environment (lines 648-650) a slaughter house is a receiving environment (as it is an environment into which the chickens are released and may escape from), implying there is a release into an environment. This to illustrate it is not clear to us what is meant with “a release of the live animal into the environment”. Can this be clarified? - Line 397: In this line “manure” is considered as animal waste, while in other parts of the document it is seen as an animal by-product. The latter interpretation would be in line with Article 2 of the Regulation defining an animal by-product (Regulation No. 1774/2002) as any part of an animal carcass, or any material of animal origin, not intended for human consumption. ‘Faeces and urine’ or ‘excreta’ would be preferable wording to use in case one refers to waste. We propose to be consistent is the use of the term by-product, to clarify which by-products (and/or waste) EFSA considers to be important in the ERA (we gather this would only be those containing recombinant DNA, the expressed DNA (RNA, protein) or the trait) and to change 3) into “indirect exposure via the use of GM animal by-products used for non-food/feed purposes (e.g. manure as fertilizer)”. - Line 438: We propose to delete the word “specific”, as ‘hypotheses’ are implicit specific. - Page 11, Table 1: The documents are poorly referenced and therefore difficult to find. In the legend, it should be written "Directive 2001/18/EC specifically applies to GMOs" rather than "Directive 2001/18/EC specifically applies to GM animals".

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452	Belgian Biosafety Advisory Council	BEL	2. Strategies for the ERA of GM animals	- Lines 287-289: We propose to replace “Therefore” by “In conclusion”; to delete “and technical data”, as it is not clear to us what is meant with this opposed to scientific data and to replace “and on common methodology for the identification, gathering and interpretation of the relevant data” by “and by using the methodology as described in Directive 2001/18/EC”, as this concluding paragraph should capture all the RA principles and not solely the step-by-step approach (which to our understanding is only referred by the words for the identification… of data). - Line 315: states “The ERA… seeks to deploy… methods and approaches to compare the GM animal… with their non-GM comparators…”. Which methods and approaches are referred to here? According to line 304 there is just one comparative approach. We thus propose to delete § 315-319 as it does not add much new information to § 302-306. - Lines 321-325: states “In an ERA, it could be useful to… assess differences associated with the GM animal in the different receiving environment”. We find this a confusing sentence: while earlier it is mentioned that the comparative approach is a key element, now it is said that assessing differences could be useful. Further, it is said “Familiarity might also derive from…”. As no explanation is given of what familiarity is in the preceding sentence, this sentence is of little relevance. We thus propose to revise § 320-325 and suggest to change this paragraph to “In an ERA, it is appropriate to draw on previous knowledge of and experience with non-GM animals (e.g. irradiated sterile mosquitoes) and from previous applications for similar GM and non-GM traits and GM constructs in similar or different animals.”
453	Belgian Biosafety Advisory Council	BEL	1. Scope of this Guidance Document	Line 259 (editorial comment): replace “animal with vertebrae” by “animal within the vertebrata".
454	Belgian Biosafety Advisory Council	BEL	1. Scope of this Guidance Document	- Page 8, line 253: Only the cold tolerance is considered here. Future applications may also concern other kind of stress such as heat tolerance, salinity or any kind of stress including the susceptibility to pathogens.
455	Belgian Biosafety Advisory Council	BEL	Summary	- Line 31: states that the document provides guidance to risk assessors, while line 213 states the document provides guidance to applicants. Shouldn’t both risk assessors and applicants be mentioned each time? The abstract (lines 16-17) state that GD is meant for both groups? - Lines 78-79: We propose to replace “Therefore” by “In conclusion”; to delete “and technical data”, as it is not clear to us what is meant with this opposed to scientific data and to replace “and on common methodology for the identification, gathering and interpretation of the relevant data” by “and by using the methodology as described in Directive 2001/18/EC”, as this concluding paragraph should capture all the RA principles and not solely the step-by-step approach (which to our understanding is only referred by the words for the identification… of data).
456	Belgian Biosafety Advisory Council	BEL	Abstract	Line 8: We propose to define better and more up front in the abstract which GM animals will be considered in this GD. We suggest the following for line 8 “… (GM) animals, namely GM fish, insects, mammals and birds, to be released…”.
457	Belgian Biosafety Advisory Council	BEL	Assessment	General comment. The document does not address the risk/benefit question. This is an important aspect when it comes to applications like GM insects to fight against vectors of humans diseases. The risk/benefit questions could be raised in a separate EFSA document.
458	Belgian Biosafety Advisory Council	BEL	Assessment	General comment. We welcome the fact that rationales are added to the data requirements (which were missing in the first GDs), but we also want to note that the scope of some GDs is getting lost: namely giving guidance on data requirements. As is the case with the GD on GM animals, sections often contain too much text so that one needs to search for the main ideas and data requirements. We ask EFSA to concise it’s GD on the ERA of GM animals, to focus more on the guidance and to restrict the content to ‘need to know’ information. We consider this important if we want to keep the GDs as tools to aid us in the evaluation of RAs. - We also want to note that the approach to give guidance differs between the different sections covering GM animals. We would welcome a more streamlined approach. - It is not clear enough from the GD what “a release of the live animal into the environment” covers. This should be made clearer in order to avoid different interpretations of what a release into the environment is (see detailed comments to lines 382 and 392).
459	Belgian Biosafety Advisory Council	BEL	Assessment	General comment. The document would gain in clarity and conciseness, and would better reach its guiding objective by limiting its content to considerations that are specific for the ERA of GM animals. General considerations about the risk assessment (such as steps in the ERA, uncertainty analysis, in fact almost all considerations before section 4) could be the topic of a separate EFSA background document which would serve as explanatory document for all types of risk assessments.

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460	Belgian Biosafety Advisory Council	BEL	Assessment	General comment. We think that this document is well prepared and made a quite complete analysis of the question. It is a great job and good base for the organization of the evaluation of GM animals. However, we have some comments and thoughts. Concerning the concept of fitness. The term is defined very generally in the glossary on page 172 and it comes up regularly in the text. It is particularly asked to assess changes in fitness experienced by GM organisms. The notion of fitness is complicated and we think it is necessary to provide indicators of fitness that are to be evaluated, such as survival, age at first reproduction and development time, fecundity, size, dispersal abilities, mating performance, the survival of the next generation, and sex ratio for example. Throughout the document there is a confusion between ecosystem services and ecosystem functioning. These are two different concepts that would need to be better distinguished in the text and not to be used the one for another.
461	Ministry of Infrastructure and the Environment	NLD	Step 2: Hazard characterisation	4.3.5. Interactions of the GM mammals and birds with non-target organisms Figure 9, p. 139 If one follows the flow diagram in Figure 9 and the text in this Chapter, multitrophic interaction should always be determined if 'it is feasible to experimentally investigate these multitrophic interactions on the focal NTO'. Can EFSA explain why multitrophic interactions should always be studied, and not only on a case-by-case basis? Should multitrophic interactions also be studied if the animals are held in captivity or semi-captivity?
462	Ministry of Infrastructure and the Environment	NLD	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Further requirements for modeling r. 4639 This part on modeling seems also applicable to the other categories of animals (fish, insects). It is therefore suggested to include a separate part about modeling and its requirements in the beginning of the opinion
463	Ministry of Infrastructure and the Environment	NLD	4.1.2 Horizontal gene transfer	4.1.2 Horizontal gene transfer HGT is expected to be rare for fish, insects and mammals/birds, still it gets quite some attention in the opinion. Also the aspects to be taken into account for HGT and the level of detail are different for HGT of fish, insects and mammals/birds
464	Ministry of Infrastructure and the Environment	NLD	3.8 Aspects of GM animal health and welfare	3.8 Welfare of animals We wonder why health and welfare of animals are taken into account in the environmental risk assessment of animals. What if there are indications that welfare is less, how would this be taken into account in the safety assessment? Should this aspect not be assessed separately? How do welfare aspects relate to mandatory animal trials for comparative purposes?
465	Ministry of Infrastructure and the Environment	NLD	3.7 Uncertainty analysis	3.7 Uncertainty analysis Although we recognize the importance of addressing uncertainties in the ERA, we wonder why there is such an extensive chapter on this subject in this opinion. This section was not part of the ERA for plants; does this mean that uncertainty plays a more prominent role for GM-animals than for GM-plants?
466	Ministry of Infrastructure and the Environment	NLD	3.5.1 General Principles	3.5.1 General pricnciples p.31 r. 1145 Is it really up to the applicant to consider which minimum effect could potentially lead to environmental harm and that the applicants thus determines the limit of concern?

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467	Ministry of Infrastructure and the Environment	NLD	3.5.1 General Principles	3.5 Experimental design and statistics 3.5.1 General principles How does statistics apply to the example of the GM cat (r. 1159) in relation to the proof of difference and proof of equivalence? How does one proof the equivalence for behavior in animals? And how does the mentioned cat experiment relate to an assessment of environmental safety of animals?
468	Ministry of Infrastructure and the Environment	NLD	3.4 The use of non-GM surrogates	3.4 Use of non-GM surrogates Although we understand the rationale to use GM-surrogates to determine its impact on the environment, it seems contradictory to obtain de novo data with the surrogate (r. 1087-1089) to determine whether there will be an environmental risk or not. Would the behavior and the potential environmental risk not be the same for the surrogate animal whether it is GM or not? If yes, the experiment could create harm to the environment. Can data from environmental experiments with surrogate species completely replace data from GM animals? How will unintended effects in the GM animals be taken into account if one makes use of surrogate species for environmental experiments? In which case are surrogate species suitable for use as a replacement for GM species in environmental experiments?
469	Ministry of Infrastructure and the Environment	NLD	3.3.1 Choice of comparators for ERA of GM fish	3.3.1. r. 1023-1027 Can EFSA explain why there would be difference between the genetic consequences of interbreeding between GM fish and wild relatives and those of non-GM, domesticated fish with wild relatives?
470	Ministry of Infrastructure and the Environment	NLD	3.2 Experimental environment	3.2. Experimental environment This section does not have an added value and most aspects are already covered in 3.5.2 (experimental design)
471	Ministry of Infrastructure and the Environment	NLD	2. Strategies for the ERA of GM animals	General comments The Dutch CA under Directive 2001/18/EC welcomes the EFSA opinion on the environmental risk assessment of GM animals. The document is quite comprehensive and addresses all potential aspects that could be taken into account in the ERA of fish, insects and animals (mammals and birds). However, the opinion shows quite some redundancy and the text does not seem to be streamlined among the different sections. Also the level of detail differs between the sections. As also indicated by COGEM, the opinion could be helpful in the ERA of animals but in its current form the opinion does not seem suitable to function as a guidance for notifiers and risk assessors. To act as a guidance, the opinion should preferentially contain a short section on the basic principles of risk assessment followed by a guidance indicating the requirements per category of animals in which it is taken into account whether the animals are kept in captivity or not. It should be clearly indicated what kind of information should be given as a minimum for each identified hazard and for each of the 5 steps in the ERA. Per trait, additional requirements can be given in a structured way using a format that is comparable between the different categories of animals. An example is the way in which the chapter on mammals and birds is structured.

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472	none	GBR	Background as provided by the European Commission and EFSA	I am commenting on the background lines 165 to 168, and stating that the EFSA is not competent to assess environmental risks as it has no remit or expertise in this area. This EFSA consultation is very poorly written. What is covered and some definitions are different in each section (for fish, insects and mammals and birds) and the structure of the report assumes it is possible to separate the effects of a GM animal from one species to another, as if multiple species did not interact in the environment. Many scientific references are missing. Potential negative effects of GM animals: Transfer of allergenic genes. Transfer of antibiotic resistance. Genes can end up in unexpected places. Genes can mutate with harmful effect. "Sleeper" genes could be accidentally switched on and active genes could become "silent". Interaction/breeding with wild and native populations. Negative impact on birds, insects and soil biota. The research in the field of genetic engineering is in preliminary stages; nothing can therefore, be said clearly about how exactly the modifications/alterations would affect the future generations of the species in questions. Gambling with the fate of these innocent creatures and ultimately human beings (who consume these animals) is not at all worth the risk. I strongly oppose ANY creation of GM animals. It"s not safe or wise and there is no way to guarantee the health and safety of people, the environment and the GM animals.
473	Food & Water Europe	GBR	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	We are extremely concerned that the guidance states, “Alteration to management practices might provide both environmental benefits as well as harm so that the net environmental impact of the overall production system needs to be considered.” (lines 4092-4094) Searching for “benefits” of GM animals is not part of a legitimate risk assessment, this is a serious alteration in EFSA’s remit (to oversee risk assessment, not to facilitate benefit analysis), and it is a disturbing indication that the conflict of interest between the regulator and applicant is already skewing what should be the scientific nature of any risk assessment in favour of the industrial interests of the applicants.
474	Food & Water Europe	GBR	2.1.3 Step 3: Exposure characterisation	Although a number of claims are made for GM salmon in the US, they are fundamentally an extension of industrial factory farming and do nothing to address the chronic problems with that type of food production. GM traits bred into animals aim to increase profit and do not address the causes of the primary problem with factory farms: stress on animals that leads to increased use of hormones and antibiotics, in turn exacerbating the problem of antibiotic resistance and unnecessarily exposing consumers to increased risk, including as a breeding ground for virus mutations and the rapid spread of diseases and contamination to spread not just among livestock but in farm workers and other people in contact with those animals. (Graham, Jay P. et al. “The animal-human interface and infectious disease in industrial food animal production: rethinking biosecurity and biocontainment.” Public Health Reports, vol. 123. May-June 2008 at 284; Pew Commission on Industrial Farm Animal Production. “Putting meat on the table: industrial farm animal production in America.” April 2008 at 23) Industrial factory farming is closely linked to a host of animal health problems including lameness, decreased bone density and infections, as animals’ bodies are pushed to increased levels of growth or milk production in tightly confined spaces. (Greger, Michael. “Transgenesis in Animal Agriculture: Addressing Animal Health and Welfare Concerns.” Journal of

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				Agricultural Environmental Ethics. September 13, 2010) The U.S. National Research Council (NRC) acknowledged this, noting in 2002, "Indeed, it is possible that we already have pushed some farm animals to the limits of productivity that are possible by using selective breeding, and that further increases only will exacerbate the welfare problems that have arisen during selection." (National Research Council of the National Academies. Committee on Defining Science-based Concerns Associated with Products of Animal Biotechnology, Committee on Agricultural Biotechnology, Board on Agriculture and Natural Resources, and Board on Life Sciences. "Animal Biotechnology: Science-based Concerns." 2002 at 106) These are among the many reasons GM animals are fundamentally unacceptable in and of themselves, but since the chemicals, drugs, water, waste and other inputs and outputs from all industrial factory farming eventually end up in the wider environment, any truly meaningful environmental risk assessment of GM animals must look at the risks for immediate and cumulative impacts of adding GM animals to an ecosystem already overstressed by industrial agriculture. We suggest again that this is not possible, so the precautionary principle indicates GM animals should not be permitted.
475	Food & Water Europe	GBR	2.1.2 Step 2: Hazard characterisation	The concept of "substantial equivalence" (EFSA Panels on GMO and AHAW (2011) at 9, Line 33) is troubling because it closely resembles the FDA's "Generally Recognized as Safe" (GRAS) distinction, which grants GRAS determinations to GM-derived foods considered equivalent to the structure, function or composition of food that is currently considered safe. (21 CFR 170.30; Pew Initiative on Food and Biotechnology (2001) at 21) This approach is not scientifically sound, undermines claims to scientific rigor and can lead to real problems. In GM salmon the FDA's comparative assessment revealed substantial nutritional differences between GM salmon and its natural counterpart, including differences in chemical composition of the meat greater than 10 percent in several vitamins and minerals and one amino acid, (Food and Drug Administration Center for Veterinary Medicine (2010) at 88-89) and statistically significant differences in levels of another amino acid, (Ibid. At 89) niacin, magnesium and folic acid. (Ibid. At 88) Despite this substantial inequivalence, the FDA still inexplicably considers GM salmon safe and dismisses the need to investigate either the causes of the inequalities or the existence of others. The EU must consider each GM animal to be a novel organism, significantly different from their natural counterparts with potentially novel risks for the wider ecosystem. Any chemical or compositional differences in any GM animal must be assessed as possible risks for the wild food web, as humans are not the only potential consumers (escapees in the case of fish being a significant concern, and other destinations of food waste – like pet food or landfill – are entirely foreseeable if GM animals are permitted). We suggest this is unfeasible and so is another reason GM animals should not be permitted.
476	Food & Water Europe	GBR	2. Strategies for the ERA of GM animals	The guidance is fundamentally flawed. For instance, it sets out a requirement for analysis to be based on "available scientific and technical data" including "unpublished research data, scientific publications, scientific and expert opinions" (lines 289-291), but it is unclear how EFSA intends to determine that all relevant data has been brought to bear given the vast scope of subject matter, the basic conflict of interest of applicants to choose favourable comparators and/or exclude unfavourable information from their submission(s) and the historical reluctance to accept or reproduce the findings from studies it considers deficient in some way. In any event attaining a high degree of precision when tackling uncertainties is an unrealistic expectation. (EFSA Panels on GMO and AHAW(2011) at 34) In this way EFSA is in effect setting a standard it cannot realistically ensure is met, so is setting itself and/or other regulators up to fail an impossible task, with errors resulting in potentially grave environmental damage.
477	Food & Water Europe	GBR	1. Scope of this Guidance Document	We have considerable concern that the EU may repeat mistakes made by others in attempting to regulate GM animals when a ban on their use for food would be a better option. The US approach to GM salmon is a good case in point, as the wider environmental risks have not been sufficiently assessed in determining the animals "safe". As noted above, current proposals suggest data submitted by the company seeking authorisation for its products, an approach used by the FDA, which in the case of biotech company AquaBounty's GM salmon lead to the FDA relying almost exclusively on only four studies (three of which are non-peer-reviewed studies submitted by AquaBounty). All of the studies exhibit great weaknesses in design, as many of the critical data sets included only a handful of fish (Food and Drug Administration Center for Veterinary Medicine (2010) at Tables 15, 16, and 29) (only six GM salmon were used to determine the allergenic potency of the fish, for example - Ibid. at 98 and 103), and AquaBounty's scientists "unblinded" the subjects of its study at one point in a clear violation of fundamental scientific method. (Ibid. At 98 and 100) This once again calls into question the regulatory agency's reliance on data provided only by the company, and the EU should not follow in the same vein in reflecting on the environmental risks of GM animals.

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478	Food & Water Europe	GBR	Background as provided by the European Commission and EFSA	We note lines 184-187 sets limits on what will be considered and what will not. We consider this draft guidance to be a hasty attempt to meet the demands of an unethical market development that would better be met with a ban on its products. Even the WTO accepts the notion of the need to protect public morals, yet it is very difficult to see where the EU is undertaking the moral and ethical discussion that should have been a prerequisite to this exercise, and would have precluded it. The current problems arising from the release of GM plants should be sufficient warning that we travel down this road at our peril – our "science" is not sufficiently sophisticated to predict or control the effects of our attempts to improve on nature. Nor are our regulatory systems sufficiently rigorous to keep GM animals off the market when they shouldn't be there, as has already been amply demonstrated. For example between 2001 and 2003, the University of Illinois allowed at least 386 GM pigs from a study to be slaughtered and sold for human consumption, even though GM pigs have never been approved for human consumption in the United States,(USDA-Office of Inspector General. "Controls over Genetically Engineered Animals and Insect Research." Audit Report. May 2011 at 14) and the release of cloned cattle into the UK food chain in 2010 highlighted the fragility of the systems in the EU.
479	Food & Water Europe	GBR	Summary	Presumably in an attempt to address some of the problems we will outline, the draft guidance requires "explicit uncertainty analysis" (lines 44-45). Human beings do not have a good record on introducing animals into new habitats. From rabbits in Australia to signal crayfish and grey squirrels in the UK, human interference in natural systems, both deliberate and unintentional, has come at a considerable cost to existing ecosystems and effort to control the damage no one foresaw. Since GM animals are unnecessary, any serious "explicit uncertainty analysis" should exclude their release into the open environment, including any farming methods that could lead to escape into the wider environment, precisely because it is impossible to predict all risks, permutations and impacts on complex living systems, particularly as they adapt to a changing climate and other pressures (including other human activities).
480	Food & Water Europe	GBR	Abstract	GM animals are unnecessary and repugnant to EU citizens. We object to the development of guidance for environmental risk assessment of GM animals as an unnecessary, unwanted reaction to the unreasonable demands of the market and therefore a waste of resources. Furthermore in this time of financial austerity and uncertainty, it is extremely difficult to justify expenditure on such processes, particularly when initial moves toward GM animals (including clones) have faced opposition from consumers and subsequently fishery industries in the US and EU. (Gibbs, Walter. "Europe scorns 'supersalmon' as GM battle widens." Reuters. April 22, 2011; Seidman, Andrew. "FDA faces opposition over genetically engineered salmon." Los Angeles Times. July 31, 2011) The funding used here would be far better spent in other ways, including banning GM animals and food from them in the EU and in imports and improving extension services and research in soil science and locally adapted breeds and feeds to improve EU food sovereignty. This draft guidance attempts to build a scientific structure around, and thereby validate, a fundamentally unacceptable practice, an exercise which is in itself unacceptable. Due to the high levels of uncertainty and risk, we cannot see how GM animals can safely be approved or enter the food system or the wider environment in which agriculture operates. This is the last gasp of an approach to animal husbandry that is driven purely by profit motives and the line should be drawn. Even the market is collapsing: the herd of GM Enviropigs was slaughtered in June due to loss of project funding and failure to find a replacement. There is no need or want for GM animals. For a fuller examination of the scientific deficiencies of the current proposals, we recommend and support the submission to this consultation by GeneWatch UK.
481	none	IRL	Background as provided by the European Commission and EFSA	EFSA is not competent to assess environmental risks as it has no remit or expertise in this area.
482	Personal	GBR	3.6.1 Categories of long-term effects	Say NO to GMO and GMA as the long term affects are not fully considered! We are risking human lives more than we can dare consider. Please read this link to gain some insight into the disaster than we are creating! http://birthofanewearth.blogspot.com.au/2011/08/gmo-foods-and-damage-to-human-babies.html?m=1
483	Personal	GBR	Step 6: Overall risk evaluation and conclusions	Say NO to GMO and GMA as the long term affects are not fully considered! We are risking human lives more than we can dare consider. Please read this link to gain some insight into the disaster than we are creating! http://birthofanewearth.blogspot.com.au/2011/08/gmo-foods-and-damage-to-human-babies.html?m=1

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484	Friends of the Earth US	USA	2.1.6 Step 6: Overall risk evaluation and conclusions	Misuse of legal power by redefining the environmental impact assessment (Lines 552-554) The guidance attempts to redefine and disregard the precautionary principle, a cornerstone of EU environmental law as defined by paragraph 2, article 191 of the Lisbon Treaty. EU directive 2001/18 aims to implement the precautionary principle when assessing potential adverse effects of GMOs. This attempt to redefine and disregard the precautionary principle can be seen in a number of places throughout the guidance. This is done though illegitimate attempts to redefine the potential adverse effects of GMOs into possible positive effects. This contradicts major EU law and EFSA has no legitimate power to change major EU laws. Examples of this can be found in a number of places throughout the guidance, including: - "Applicants should indicate why these levels of risk might be acceptable in assessing the net overall environmental impact of the GM animal." (lines 552-554) - Alteration to management practices might provide both environmental benefits as well as harm so that the net environmental impact of the overall production system needs to be considered. (ines 4092-4093) - "The applicant should evaluate under which circumstances any changes resulting from the specific GM management and production systems may lead to greater, similar or lower adverse environmental effects than the current system." (Lines 6097- 6099) While possible environmental benefits are an important part of conducting a cost-benefit analysis of any action or approval, an environmental risk assessment is not a cost-benefit analysis nor is it a risk management plan. According to the European Commission's own definitions: "Risk assessment is a scientifically based process comprising four steps: hazard identification, hazard characterization, exposure assessment and risk characterization… Within the Commission there is a functional separation between risk assessment and risk management. This is essential in order to protect the scientific integrity of the risk assessment process and to ensure an appropriate balance of the various factors that affect risk management choices." It is outside the parameters of this guidance on environmental risk assessment to redefine what and how risk assessments are conducted.
485	Friends of the Earth US	USA	2.1.5 Step 5: Risk management strategies	(line 509 – 563) The guidance has substantial gaps in the proper implementation of major requirements of the EU's directive 2001/18. For example, the description of the steps in the risk management strategy is narrowed to the presentation of data and assessment by the applicants themselves while EFSA assessment is not mentioned at any point. A major weakness is that the guidance does not foresee that a GM animal could be assessed as too risky for an authorization and that EFSA might recommend to the European Commission not to authorize it. This leads us to the conclusion that the main aim of a new guidance is to assess GM animals as safe and this contradicts the relevant article 13 in directive 2001/18 and must be corrected.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
486	Friends of the Earth US	USA	1. Scope of this Guidance Document	No guidance on ERA requirements for GM animals intended for export and open release (line 213-214) This document fails to provide guidance on the requirement to conduct an ERA for GM animals and insects intended for export and open release outside the EU, and EU law mandates that ERAs for GMOs must meet EU standards when intended for export. Regulation (EC) No 1946/2003 of the European Parliament and of the Council on Transboundary Movements of Genetically Modified Organisms from 2003 incorporates the Cartagena Protocol on Biosafety to the Convention on Biological Diversity into European law. According to Regulation (EC) No 1946/2003, "exports of genetically modified organisms intended for deliberate release into the environment should be notified to the Party or non-Party of import, allowing it to make an informed decision, based on a risk assessment carried out in a scientifically sound manner." This risk assessment must be consistent with Annex II to Directive 2001/18/EC which outlines the standards and methodology to be followed for any Environmental Risk Assessment in the European Union or for any GM product intended for export. In other words, any export of a GM animal or insect must go through an ERA that meets EU standards before they are exported to a country outside the EU. This is particularly relevant in the case of GM insects as the leading GM insect company, Oxitec, is based in the United Kingdom and has already exported its GM mosquitoes to the Cayman Islands, Malaysia, and Brazil and hopes to expand exports to the United States, India, and elsewhere. In fact, Oxitec is currently working with the Florida Keys Mosquito Control District to seek approval from the Food & Drug Administration for the deliberate release of GM mosquitoes into the environment. As this guidance is intended to outline how ERAs are conducted on GM animals and insects within the EU, and any export of GMOs must meet the EU standards for ERAs, the applicability of this guidance to the export of GMOs, as outlined by the Cartagena Protocol on Biosafety and Regulation (EC) No 1946/2003, are very relevant and are currently ignored.
487	Friends of the Earth US	USA	1. Scope of this Guidance Document	No guidance on ERA requirements for GM animals intended for export and open release (line 213-214) This document fails to provide guidance on the requirement to conduct an ERA for GM animals and insects intended for export and open release outside the EU, and EU law mandates that ERAs for GMOs must meet EU standards when intended for export. Regulation (EC) No 1946/2003 of the European Parliament and of the Council on Transboundary Movements of Genetically Modified Organisms from 2003 incorporates the Cartagena Protocol on Biosafety to the Convention on Biological Diversity into European law. According to Regulation (EC) No 1946/2003, "exports of genetically modified organisms intended for deliberate release into the environment should be notified to the Party or non-Party of import, allowing it to make an informed decision, based on a risk assessment carried out in a scientifically sound manner." This risk assessment must be consistent with Annex II to Directive 2001/18/EC which outlines the standards and methodology to be followed for any Environmental Risk Assessment in the European Union or for any GM product intended for export. In other words, any export of a GM animal or insect must go through an ERA that meets EU standards before they are exported to a country outside the EU. This is particularly relevant in the case of GM insects as the leading GM insect company, Oxitec, is based in the United Kingdom and has already exported its GM mosquitoes to the Cayman Islands, Malaysia, and Brazil and hopes to expand exports to the United States, India, and elsewhere. In fact, Oxitec is currently working with the Florida Keys Mosquito Control District to seek approval from the Food & Drug Administration for the deliberate release of GM mosquitoes into the environment. As this guidance is intended to outline how ERAs are conducted on GM animals and insects within the EU, and any export of GMOs must meet the EU standards for ERAs, the applicability of this guidance to the export of GMOs, as outlined by the Cartagena Protocol on Biosafety and Regulation (EC) No 1946/2003, are very relevant and are currently ignored.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
488	Friends of the Earth US	USA	4.2 Specific areas of risk for the ERA of GM insects	EFSA lacks competence to assess environmental risks of genetically modified insects for agriculture or vector control as it has no remit or expertise in this area. While the safety of food products derived from genetically modified animals would fall under the purview of EFSA, the environmental risks would be better assessed by an agency with specific expertise in environmental risk, entomology, insect ecology, etc. A similar situation exists in the U.S. in which the Food & Drug Administration (FDA) is currently reviewing applications for the field release of genetically modified mosquitoes in the Florida Keys. The FDA certainly has expertise in veterinary medicine but it too lacks appropriate expertise to properly assess the full range of risks GM insects pose to the environment or human health. Similarly, these issues fall completely outside the purview of EFSA and would better be addressed by more relevant agencies such as the Environment Agency, the European Medicines Agency, the Executive Agency for Health and Consumers, and the European Centre for Disease Prevention and Control, and other relevant agencies from member states. Expertise in entomology, epidemiology, insect ecology, and other relevant fields would be necessary to properly assess the environmental risks of using GM insects for agriculture applications or as a means to fight disease – expertise that the EFSA currently lacks.
489	Friends of the Earth US	USA	4.1.6 Environmental impacts of the specific techniques used for the management of GM fish	The draft guidance fails to properly consider the environmental impact from feeding GM fish in commercial operations. Fish farming already poses a major threat the health and survival of wild fisheries and the expansion of GM fish industries is likely to exacerbate this problem. For example, AquaBounty's GM salmon is engineered to be fast growing and therefore may require up to five times more food than its non-GM counterpart (See: Abrahams, M.V. and A. Sutterlin (1999). The foraging and antipredator behaviour of growth-enhanced transgenic Atlantic salmon. Anim. Behav. 58: 933-942). Salmon are carnivorous and therefore high up on the food chain so they require large amounts of wild-harvested fish. Total amounts of fishmeal and fish oil needed to feed farmed salmon rose from 261.4 thousand tons to 982 thousand tons between 1992 and 2003, respectively, a number that has no doubt increased since then as the number of farmed salmon have also increased. According to a report from the United Nations' Food and Agriculture Organization, 50% of the world's fish oil is used as feed for farmed salmon. Roughly one-third of all small "forage" fish – such as anchovies, sardines, and menhaden – are caught to feed farmed salmon. Farmed salmon typically need to consume three pounds in order to gain a single pound. Seafood species populations are already on the brink of collapse. Any further increased pressure on marine ecosystems – such as GE fish that require up to five times more feed – poses a serious threat to not only the wild populations of fish and seafood but global marine ecosystems as a whole. Not only does feeding smaller fish to larger farmed fish deplete wild populations but their harvesting has also been shown to deplete natural habitats for these fish, further diminishing their numbers.
490	Friends of the Earth US	USA	4.1 Specific areas of risk for the ERA of GM fish	The problem formulation for assessing risks of GM fish (line 1906) is posed as: "Will GM fish be released or escape and survive outside rearing system?" If the answer to this question is no, then the risk assessment is to be confined to the impacts of GM fish in managed systems. This formulation is inherently problematic in that it assumes the petitioner can predict, and will honestly report, if escapes from the production systems are possible, expected or planned. Fish escape from commercial facilities on a regular basis. As Atlantic salmon is the closest GM fish to commercialization in the world, it would be useful to look at escape rates of farmed salmon to illustrate this issue. For example: up to 2 million Atlantic salmon escape fish farms in North America every year; in 2002, 600,000 salmon escaped from pens in the Faeroe Islands during a single storm; one million farmed salmon escaped from a Chilean fish farm during a single incident in 2004; and in 2006, nearly half a million salmon escaped from a single Norwegian salmon farm. Proponents of GM salmon (notably AquaBounty) will argue that GM salmon will only be raised in inland tanks and therefore there is no risk of escape into local rivers, estuaries, or oceans. Unfortunately, there are no legal requirements that GM salmon only be raised in inland tanks and a vast majority of salmon farming around the globe occurs in open ocean net facilities. It must be assumed that GM fish will eventually be produced in these facilities and in turn ultimately escape into the wild. The EU experience with field trials of GM rape seed, for example, showed that the pollen and seeds were disseminated. The EU directive 2001/18 foresees that broader socio-economic aspects of the use of GMOs should be reflected. Food safety agencies (such as EFSA and the U.S. FDA) do not have the legal authority or capacity to ensure that all GM fish are only raised in

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				contained inland tanks, especially if operations are working at a commercial scale. Additionally, these agencies do not have the capacity to track the fish once they are sold to growers around the world to ensure every grow-out facility follow legally mandated biosafety protocols. Allowing the GM fish industry to determine on its own if they expect an escape to occur is akin to allowing the oil industry to determine if an oil spill will occur and frame the risk assessment accordingly (which, unfortunately, the oil industry is allowed to the in the United States).
491	Friends of the Earth US	USA	Background as provided by the European Commission and EFSA	EFSA lacks competence to assess environmental risks of genetically modified insects for agriculture or vector control as it has no remit or expertise in this area. While the safety of food products derived from genetically modified animals would fall under the purview of EFSA, the environmental risks would be better assessed by an agency with specific expertise in environmental risk, entomology, insect ecology, etc. A similar situation exists in the U.S. in which the Food & Drug Administration (FDA) is currently reviewing applications for the field release of genetically modified mosquitoes in the Florida Keys. The FDA certainly has expertise in veterinary medicine but it too lacks appropriate expertise to properly assess the full range of risks GM insects pose to the environment or human health. Similarly, these issues fall completely outside the purview of EFSA and would better be addressed by more relevant agencies such as the Environment Agency, the European Medicines Agency, the Executive Agency for Health and Consumers, and the European Centre for Disease Prevention and Control, and other relevant agencies from member states. Expertise in entomology, epidemiology, insect ecology, and other relevant fields would be necessary to properly assess the environmental risks of using GM insects for agriculture applications or as a means to fight disease – expertise that the EFSA currently lacks.
492	Oxitec Ltd	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 4220-4295 Loss of immunity in the human population and reliance on continued long term positive effects of the suppression of the vector species. This assessment of potential delayed effect is not required for a pesticide, biocontrol organism or other pest control method that could have the similar effect, and as the effects will only be picked up if vector population suppression is effective, this should be picked up in case specific post market monitoring.
493	Oxitec Ltd	GBR	4.2.6 Impact on Human Health	There are several typographical errors, too numerous to comment on in this section that need correction.
494	Oxitec Ltd	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 4067 -4069 For example, additional applications of pesticides may be needed to manage program failures and to control the untransformed insects. These may cause novel environmental loads and /or decrease of sustainability of the system. We question how many layers of “what if” scenarios does an applicant need to pursue ? Novel environmental loads and system sustainability for the pesticide should not be loaded onto these products. There are other regulatory systems dealing with pesticide use.
495	Oxitec Ltd	GBR	Step 4: Risk characterisation	lines 3973 -3975 Evidence suggests that there has been significant latitudinal and altitudinal range expansion or retraction within the EU across a wide variety of species due to climate change. Expansion and retraction of species due to climate change is not static and is still happening, so how can a change be attributed to the use of the GMO.
496	Oxitec Ltd	GBR	Step 4: Risk characterisation	Line 3586 -3590 Knowledge of the ecology (dynamics of temporal patterns of distribution and abundance) of principal pests/ vectors in the area of GM insect releases should consider characterising the spatial pattern and the scale of the risk. It is very unclear what this actually might mean for the applicant. More guidance should be provided here.
497	Oxitec Ltd	GBR	Step 1: Problem formulation (including identification of hazard and exposure	Line 3489-92 There may be physiological impacts of introducing large numbers of novel individuals in a release programme, for example allergic reactions to mosquito biting may be greater when people are exposed to a new population of a target mosquito species derived from another location. The example appears without any evidence for its basis. If there is evidence that this is a potential risk then this should be cited. If not, then a causal chain should be included in the example.

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			pathways)	
498	Oxitec Ltd	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 3354 In the short term, populations in this area may be increased by releases of significant numbers of GM insects…… Some of these statements implicitly assume that the released GM insects BECOME part of the wild insect population, rather than (conceptually) existing alongside it. We don't think this leads to any unreasonable conclusions, but it might cause confusion (e.g when GM male insects are released, does that mean the wild population increases ?)
499	Oxitec Ltd	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 3159 -3161 We suggest to insert for such elements immediately after the words segregation rate as the present text could imply that such information is required for all GM insect applications. Accordingly the proposed revised text is suggested: For instance gene drive systems are considered tools for vertical dissemination of DNA inserts about above the expected Mendelian segregation ratios, for such elements
500	Oxitec Ltd	GBR	4.2 Specific areas of risk for the ERA of GM insects	Section 4.2 line 3001 We propose the following revised text: Cross-mating of a GM insect with non target species of subspecies complexes. If mating between a GM insect expressing a dominant mortality/lethality gene and non-target insects should occur, at a significant frequency, it could disrupt the population dynamics of these other species or subspecies leading to harm or loss of valued ecological species.
501	Oxitec Ltd	GBR	4.2 Specific areas of risk for the ERA of GM insects	Line 1483 and lines 1536 -8 Over time new management or production systems may arise. Such changes and their potential effects on the GM animal must be addressed in the application as well on a case by case basis. Applicants do not have a crystal ball and cannot see into the future. This is an excessive requirement. Any consent granted is time-limited and has post market monitoring and general surveillance requirements. Changes in management and production systems and their potential effects on the GM animal can be addressed at consent renewal where there will be supporting evidence as to what changes in management and production systems have occurred.
502	Oxitec Ltd	GBR	3.5.2 Principles of experimental design	Line 1258 Trade-offs between the transformed state and other characteristics need to be identified so that they can be examined (eg feeding – risk taking) Feeding risk taking is much more likely as a consequence of colonisation than that of transformation, and is a poor example to use.
503	Oxitec Ltd	GBR	3.5.2 Principles of experimental design	Lines 1061-2 and 1226 Since GM animals cannot be deliberately released into the environments, for which ERA is being conducted…… This sentence is very confusing for the applicant. What it appears to be implying is that the placing on the market of GM animals might be possible at some time in the future but release of GM animals in a research context is SO DANGEROUS, that it cannot go ahead. This seems to be contrary to the step-wise approach of phased testing that has been used for GM plants and other GM organisms. This is also a dangerous message to give to the rest of the world that might be looking at this Guidance. Additionally it highlights a lack of clarity between the role of this document in the preparation of ERA for Part B releases and the preparation of the ERA for Part C applications. More clarity on this topic would be desirable.

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504	Oxitec Ltd	GBR	3.1.3 Selection of the relevant receiving environments	Lines 762 -767 Furthermore applicants should take into account the potential risk implications for the presence of any other GM animals and other introduced species than have been placed on the market and released in the same receiving environments including interactions between the specific production management and control characteristics associated with the different GM animals. In addition applicants should consider likely and predicted trends and changes to the receiving environments and how these might interact with GM animals. This appears to be rather a sweeping and open ended statement of requirement to address anything that might happen in the future. It is recommended that this is time limited to the period of consent in the Directive (ie 10 years). Therefore we propose the following alternative wording: Furthermore applicants should take into account the potential risk implications for the presence of any other GM animals and other introduced species than have been placed on the market and released in the same receiving environments including interactions between the specific production management and control characteristics associated with the different GM animals. In addition applicants should consider likely and predicted trends and changes to the receiving environments and how these might interact with GM animals, during the time period of the consent (ie 10 years).
505	Oxitec Ltd	GBR	3.1.3 Selection of the relevant receiving environments	Lines 735 .. …applicants need to consider the full geographic range of the GM animal, the issues of concern and the receiving environments in which these issues occur. The example given indicates that if an NTO is at high risk from the GM animal then studies should be conducted in environments where there are/will be high numbers of the NTO affected ….to study population effects. It could be very difficult and impractical to study impacts on NTO's in the environment where you are relying on a natural population of the NTO that might be seasonal or itinerant. If there is a potential high risk to a specific NTO then this should be conducted first in a laboratory situation (assuming the NTO is amenable to laboratory culture) to determine if indeed the potential high risk is realised. If the high risk is then realised, tiered testing could then be conducted at a semi-field basis. To assess potential risk at a population level without an initial laboratory study appears to be creating the potential for more harm to the NTO population than is necessary.
506	Oxitec Ltd	GBR	3.1 Receiving environments	Lines 642-643 The ERA should be carried out on a case by case basis, meaning that the required information may vary depending on the type of GM animal concerned, their intended use and the potential receiving environments, taking into account inter alia other GMO's already in the environment. This sentence is very unclear regarding the scope for other GMO's in the environment. Does it mean that for example a release of a GM mosquito will have to consider it's impact on GM crop plants that are grown commercially, or on a GM animal for pharmaceutical production when the there is no causal risk hypothesis ?
507	Oxitec Ltd	GBR	2.2 Information to identify potential unintended effects	Lines 607-609 Therefore each GM animal must be characterised …. The term GM animal needs further definition, especially regarding GM insects eg: strain, type/ event etc. Many million GM insects could be used each week in suppression type programmes, each of these cannot be characterised individually.
508	Oxitec Ltd	GBR	2.1.5 Step 5: Risk management strategies	Lines 526 -529 For instance, appropriate management and control measures should be put in place prior to the releases into the environment of mass reared GM sterile mosquitoes in order to ensure consistency and efficacy of the release systems and the achieve the intended outcome …. This sentence appears to indicate that EFSA will be evaluating the efficacy as well as the safety of the use of GM insects. This appears to be beyond the scope of the Directive.
509	Oxitec Ltd	GBR	2.1.5 Step 5: Risk management strategies	Line 520- 523 This paragraph implies any potential risk needs mitigation measures, but then goes on to say that if the risk is not considered significant, risk mitigation might not be needed. Risk management theory indicates that risks can be accepted, mitigated, avoided or transferred, so it would be clearer to indicate that risks not deemed to be significant can be regarded as accepted/ acceptable. Otherwise the text as it stands if confusing and only considers risk mitigation.
510	Oxitec Ltd	GBR	2.1.5 Step 5: Risk management strategies	Line 513-515 Limits of concern (ie protection goals) should be set at political level and not by the applicants. Therefore even if risk management strategies are employed to reduce potential risk, as the limits are unknown or unset it could still be inadequate politicalLy or socially.

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511	Oxitec Ltd	GBR	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 392 In the case where the GM animal use does not include the release of the live animal into the EU environment nor its breeding and rearing in the EU, the problem formulation will consider the following possible routes of exposure…. For what purpose is this information required if the live animal is not deliberately released in the EU ? "just in case ??" This seems overly precautionary and potentially beyond the scope of the Directive.
512	Oxitec Ltd	GBR	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 375 -377 A comparison of the characteristics of the GM animal with those of the appropriate selected comparator (s) enables the identification of differences in the GM animal that might lead to harm. This text presumes that that the selected comparator is not in itself harmful. This is not always the case : e.g insect plant pests are already harmful to plants, as they are plant pests and genetic modification can make them less harmful. We suggest alternate text: A comparison of the characteristics of the GM animal with those of the appropriate selected comparator(s) enables the identification of differences in the GM animal that might lead to more harm than the relevant selected comparator(s).
513	Oxitec Ltd	GBR	1. Scope of this Guidance Document	Line 267-271 Applicants are advised to assess likelihood and risk by implementing principles in the guidance document on the risk assessment of food and feed for GM animals, if the animal is not intended for food/feed use It is unclear whether this is requiring a non-food/feed animal to be assessed for ingestion as if it were a food animal. Clearly this would add considerably to the cost/time/ complexity for applicants for any studies required, where accidental ingestion is likely to be at a very low threshold. A clarification that food/ feed analysis is not necessary for non-food animals would be helpful as there could be scope for considerable misinterpretation of this advice between Member States.
514	Oxitec Ltd	GBR	Assessment	lines 215-216: The Guidance has been designed to assist applicants in preparing a risk assessment. As a potential applicant we find it poorly written in parts and confusing to meet the stated aims of assistance in preparing the ERA. The addition of flow charts and diagrammatic representation of the data requirements will facilitate understanding and ease of use for applicants. It is also disappointing that the Guidance Document has based it"s approach on the Guidance Document that was prepared for the ERA for GM Plants, where many of the issues with animals are quite different and should be addressed as such.
515	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	4.3.3 Pathogens, infections and diseases	Line 5067, page 119: Editorial comment: Replace "contest" by "context".
516	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 4802 to 4880, pages 113 to 115: The selection of advantageous traits and their underlying genes in animal breeding and its potential consequences for the genetic diversity of populations of animals in production systems or companion animals is not new and not specific for GM animals. If this issue shall be dealt with, it has to be done in a broader context. In our opinion there is no reason to deal with this issue specifically in the ERA for GM animals.

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517	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 4463, page 106 Spelling error: fulfill. Lines 4532 to 4535, page 107: It is not clear how it is possible to identify a suitable “taxonomic and ecological niche-surrogate non-GM species” if “direct information on the GM parental species is not available”. The statement should be either clarified or cancelled. Line 4534, page 107 Spelling error: fulfill.
518	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 3: Exposure characterisation	Lines 4301 to 4302, page 102: Editorial comment: The sentence is not clear as the half sentence after the colon does not explain the half sentence before it. What is the tiered approach to be followed up in an exposure assessment
519	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 4213 to 4214, page 100: Editorial comment: The section uses the term “SIT” which has not been introduced before.
520	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	4.2.6 Impact on Human Health	Line 4166 to 4168, page 99. The sentence “It should be recognized that impact on human health caused by accidental ingestion of GM insects is not considered by this section” can be deleted since there is a slight contradiction to the sentence further down in line 4181 “Specific toxicity testing of the newly introduced proteins as such will not be required within the framework of this Guidance Document, but the introduction of proteins known to be detrimental to consumers should be discussed by the applicants and the intake should be avoided”.
521	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 5: Risk management strategies	Line 4031, page 96: Replace “monitoring” by “inspection” since this type of control as mitigation measure for experimental releases is different from PMEM.
522	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 2: Hazard characterisation	Line 3899, page 93: Replace “should be provided” by “should be considered”, otherwise the case-by-case principle in ERA would be violated. Line 3938, page 94: Replace “identified in the released” by “identified for the released”.
523	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 5: Risk management strategies	Line 3629, page 87: Replace “emphasis on the failure” by “emphasis also on the failure”.

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524	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 3346, page 81: It is Step 4 in the ERA that focusses on risk.. The term “risk” should be omitted in the preceding steps Lines 3349 to 3370, page 81: The chapter describes harm that may be caused by changes in the TO population after release of GM insects. This issue is not a GM-specific harm as this problem occurs with any kind of suppression or preventative release of insects. The guideline should focus on ERA relevant issues that are caused by the genetic modification. Lines 3391 to 3396, page 82, lines 3470 to 3477, page 84, and lines 4222 to 4227, page 100: Detrimental changes in human behavior as a result of suppression or prevention programs are clearly not an outcome of genetic modification of insects used in some of these programs. They are a socio-economic problem related with any kind of technical prevention campaigns. There is a clear statement in the introduction of the guidelines saying that socio-economic problems are outside the focus of the guideline (lines 250-252: “Ethics, socio-economic aspects as well as issues linked to traceability, labelling, or co-existence of production and supply systems are not addressed in this Guidance Document”). Therefore, these lines should be omitted. Lines 3346, page81, and 3432 to 3433, page 83: In these lines management systems and monitoring efforts are discussed as part of step 1 “problem formulation”. These items should be discussed rather under section “risk management strategies”.
525	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 3: Exposure characterisation	Line 2199, page 55: The term ‘Alternative sources’ needs better explanation or an example.
526	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 3: Exposure characterisation	Line 1997, page 51: “wild types” should be changed to “wild relatives” for clearity.
527	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 2: Hazard characterisation	Line 1946, page 49: Replace “assessed in the different” by “assessed for the different” Line 1967, page 50: “semi artificial” should be defined in the glossary Line 1972, page 50: The term “determine” should be specified. The sentence should not mean obligatory experimental tests independent of any indication of such changes based on trait or existing experience.
528	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Step 1: Problem formulation (including identification of hazard and exposure	Line 1895/96 page 47: It should be clarified if and to what extent the potential spread of fish diseases during import, transportation, storage, handling and processing is scope of Regulation (EC) No 1829/2003 (EC, 2003) or Directive 2001/18/EC (EC, 2001). Justification should be given and interrelation to other EU or national legislation concerning “spread of animal diseases” should be detailed. The need of additional data and risk assessments by overlapping with other regulations in place should be avoided. See also comment at lines 389 to 391.

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			pathways)	
529	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	4.1.1 Gene transfer and consequences	Line 1874ff page 47: The possibility of unchanged fitness should be considered as well.
530	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	4.1 Specific areas of risk for the ERA of GM fish	Line 1856/1857 page 47: See comments made at line 248
531	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	4. Specific areas of risk to be addressed in the ERA	Line 1827, page 46 Figure 5: In the column headed “GM mammals and birds” both, the first and second box do contain the issue “vertical gene transfer”. To avoid redundancy, the issue should be discussed in one section only. This holds true also for related sections of the GD.
532	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.8.2 Health and welfare aspects for GM fish	Line 1738 page 44, line 1798 page 45: See comments made under lines 216/217 and 235/236, page 7.
533	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.8 Aspects of GM animal health and welfare	Line 1738 page 44, line 1798 page 45: See comments made under lines 216/217 and 235/236, page 7.
534	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.5.2 Principles of experimental design	Line 1292 to 1303, page 34 to 35: Figure 4 is more confusing than helpful. The issue can be well described in words rather than using a semi-mathematical model. Figure 4 should be omitted
535	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.4 The use of non-GM surrogates	Lines 1052 ff., page 29 See comment on Lines 888 ff.

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536	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.3 Choice of comparators	Lines 881ff, page 25: Substitute “wild type” by “native types” or “wild relative” or clarify otherwise that the term ‘wild type’ has different meaning in ecology and animal breeding. This recommendation applies to the whole GD. Lines 888 ff., page 25: For the cases where the parental species of the GM animals to be released is not endemic (introduction of an alien species) it should be clarified whether the ERA according to this GD as well as the permission according to Regulation (EC) 1829/2003 or Directive 2001/18/EC replace respective permissions according to e. g. national implementations of article 22 of Directive 92/43/EEC or Regulation (EC) 708/2007. If this is the case, it should be clarified how far the part of the assessment that deals with the introduction of the GM animal as an alien species complies with the respective ERA procedures for alien species. It should be stated explicitly if the part of the ERA for GM animals that deals with the introduction of an alien species should then follow the same approaches as developed for the assessment of alien species. If the ERA should follow different approaches this should be justified. The assessment of the introduction of an alien species poses a challenge in itself. In cases where the parental species of the GM animals to be released is not endemic it therefore seems advisable to clearly separate the assessment of the consequences of the introduction of the alien species from the assessment of the possible effects of the genetically modification and possibly follow a two-step approach (see also Lines 4446 ff. on page 106 and Lines 4501 ff on page 107). It is better to combine the existing expertise in this two step procedure to improve the quality of the assessment (see our comments for Lines 231 ff, page 7) Line 904ff, page 25 Could you give an example for a GM animal/trait where such conventional counterpart would be missing (e.g. cold tolerant Glow Fish)? Lines 923/924, page 26: There may be cases where the comparison should not (only) be carried out with the state of the receiving environments prior to the release but also with the predicted state of the receiving environments if the release does not take place. An example could be the release of GM animals to control pests or diseases. Line 925, page 26: Replace “(where the conventional counterpart is not present)” by “(when the conventional counterpart is not available)”

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
537	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.2 Experimental environment	Line 793-803, page 23: It should be made clearer in this section that the GM animal is the primary focus of the ERA and not any substance. The paragraph should be re-phrased as: "Environmental risk assessment is concerned with the complexity of the organism assessed, the newly expressed GM trait and/or GM product, and their interaction with components of the environment. This complexity is generally more pronounced in animals than in plants, and less in any assessment of pure substances like pesticides. For example, animals generally exhibit more complex behaviour (and maybe sociality) than plants; the mobility of an individual animal and its population will generally exceed that of a plant within a life-time, and whereas plants are usually at the bottom of the food chain an animal may be either a predator or a prey item, or may be both. Hence, it might be expected that, firstly, the ERA of a GM animal would be more varied and complex, and encompasses a wider range of issues than the ERA of a plant. Secondly, that the mobility of animals would focus the ERA more on questions related to invasiveness and persistence and thus draw on the considerable scientific literature concerning alien species." Line 814, page 24: Substitute “For any identified risk” by “For any identified hazard”. Line 840, page 24: Substitute “However, there is a need to…” by “However, there is a potential need to…” otherwise there would be too much emphasis in conducting ‘risky’ tier 3 experimental releases of GM animals (see comment on line 735 above).
538	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.1.3 Selection of the relevant receiving environments	Line 735, page 22: We strongly recommend to clarify the meaning of the term ‚study’ for the entire document. ‘Study’ should not necessarily mean ‘experimental study’. It should be possible to conduct ‘desk studies’ in many cases, particularly where experimental environmental releases of GM animals are difficult to be contained in time and space. Line 737-741, page 22: This recommendation is problematic since it is very often not feasible to conduct field experiments under such risky conditions for the NTO(s) in question. Rephrase the sentence like: For example, if hazards for NTOs are identified, studies characterizing the risk should be conducted for the environments where there are/will be high levels of exposure of the NTOs to the GM animal. The inherent risk in case of experimental studies should be considered for conducting environmental releases for NTO populations in the study area (see also comment for line 735 above). Lines 755 to 761, page 22: In our opinion, the characterization of the GM animal and its potentially harmful characteristics should inform the decision which baselines of the receiving environments are relevant and should be established as points of reference against which future changes can be compared (see comment to lines 414 to 417, page 12)
539	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.1.2 Identification and characterization of the receiving environments	Line 712, page 21: “Use of by-products” should be replaced by “use and/or spread of by-products” to also cover unintended spread.
540	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	3.1.1 Definition of receiving environments	Line 649, page 19: “recombinant DNA” should be specified as replicable DNA in a living organism. Environments receiving free DNA should not be considered as receiving environments.

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
541	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2.3 Structural overview of this Guidance Document	Line 631 Figure 2, page 18: The arrows top-down step 2 to step 6 should start a bit further down from the top (in comparison to step 1 arrow) in order to indicate that these steps are not necessary if hazards are not identified (see line 451ff). Consider to use a different shape for step 5 indicating that risk management measures are not always applicable. Finally, the arrows for the specific areas of risk (Chapter 4) [alternatively the Figure legend] should account for the fact that the areas differ for the animal groups addressed in the Guidance document. The Cross-cutting considerations do not correspond with topics named in the specific area for fish. To ease reading an understanding an adaptation of topics should be considered (see also comments made at lines 49 to 53).
542	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2.2 Information to identify potential unintended effects	Line 569, page 16 Cancel “environmental” in this line as here unintended effects are addressed in general. Each unintended effect should be then specifically assessed for environmental effects (see last sentence of the paragraph).
543	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2.1.5 Step 5: Risk management strategies	Lines 521-522, page 15 Exchange “considered significant” by “considered biologically relevant”.
544	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2.1.3 Step 3: Exposure characterisation	Lines 480 to 486, page 14: “Likelihood of exposure” should be replaced simply by “exposure”. In our opinion exposure is best characterized by describing its nature, magnitude, frequency, and duration, and not in terms of probability.
545	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 370ff, page 11: Check whether there are more protection goals related to farm and companion animals (e.g. COUNCIL DIRECTIVE 98/58/EC concerning the protection of animals kept for farming purposes). Lines 389 to 391, page 12: The introduction of pests or pathogens of an animal into the environment if that animal is introduced or escapes into the environment is not in the first place a GMO-specific issue. It should be made clear that this issue only has to be considered in the ERA for a GM animal insofar as the introduction of pests or pathogens of the GM animal into the environment is affected by the GM trait (compared to the introduction of pests or pathogens of non-GM animals of the same species). Lines 414 to 417, page 12: “Baselines of the receiving environments, should, as far as possible and based on available data, be established before any (harmful) characteristics of the GM animal can be identified.” This sentence reads as if the overall “status quo” of the receiving environment(s) has be established to enable the definition of harmful characteristics of the GM animal. In our opinion, the decision which baselines of the receiving environment(s) need to be established should be made on the basis of characterization of the GM animal and its potentially harmful characteristics. Lines 429 to 439, page 13: It should be explicitly stated that points 5 to 10 only have to be carried out if potential adverse effects have been identified under point 4.

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546	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2.1 Different steps of the Environmental Risk Assessment	Chapter 2.1 describes in detail the different steps of Environmental Risk Assessment and the reasoning behind as outlined in Annex II of Directive 2001/18/EG. However, many subchapters of chapter 4.2 repeat in each step of the ERA information that was given in chapter 2.1 already, e.g. lines 4136 to 4142, page 98. This information should be removed to avoid redundancy. Furthermore, often there is also redundancy in the contents of the different steps of the ERA, e.g. contents of lines 3036 to 3057, page 74 is repeated in lines 3072 to 3088, page 75.
547	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	2. Strategies for the ERA of GM animals	Line 306, page 8 Add “of the genetic modification” at the end of the sentence. Line 308, page 8 Editorial comment: Spelling error: fulfill.
548	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	1. Scope of this Guidance Document	Line 248, page 8: “Commercial” should be replaced by “deliberate” or “intended”. Not all releases of GM animals into the environment will be carried out for commercial reasons. The scope of this document is ERA according to Directive 2001/18/EC (EC, 2001), and thus the wording used for the type of environmental release should be taken directly from Directive 2001/18/EC (EC, 2001). Furthermore, it should be clarified here if the unintended escape of GM animals from “contained use” facilities is covered by the GD or not. Line 269, page 8 Exchange “implementing principles in the Guidance” by “applying principles from the Guidance”
549	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Assessment	Lines 216/217 and 235/236, page 7: The scope of the document is stated to be guidance for conducting a ERA according to Regulation (EC) No 1829/2003 (EC, 2003) or Directive 2001/18/EC (EC, 2001) (Lines 213-215). However, the scope is extended here to “animal health and welfare” without clear justification. There are other EU or national legislations in place dealing with this aspect. A separate GD (EFSA, 2012a) addresses the “assessment of health and welfare of GM animals bred for food and feed use. The assessment is made in terms of the effective functioning of their body systems in a given environment.” In addition this document covers any aspect of health and welfare of GM animals for non-food/feed uses. It should be clarified why this topic is raised again in a GMO-specific context and interrelation to existing legislation should be detailed (see also section 3.8). E.g., “environmentally-related animal health and welfare aspects of GM animals” (Lines 216/217) or “aspects of the health and welfare of GM animals to be released into the environment” (Lines 235/236) should be specified as additional aspects of health and welfare of GM animals bred for food and feed use that become relevant under the specific circumstances of the intended release (in general or as a consequence of specific management measures). Lines 229/230, page 7: It should be explained why the use of GM animals for the production of pharmaceuticals is not covered in the GD. Production of pharmaceuticals will probably be one of the most important applications of GM mammals. It should also be clarified that ‘use of GM animals for the production…’ is directed to placing on the market. Lines 231 ff, page 7: Clarify whether the applicant needs additional permissions according to e. g. national implementations of article 22 of Directive 92/43/EEC or Regulation (EC) 708/2007 if the parental species of the GM animals to be released is not endemic (alien species)? If yes, these additional legal requirements should be considered in this paragraph. It should also be made clear in this chapter if the ERA and the permission according to Regulation (EC) 1829/2003 or Directive 2001/18/EC replace respective legal requirements. For clarification a short conclusion should be added on

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				how far this specific aspect of the assessment of the GM animals complies with the respective ERA procedures for alien species. This should be clarified and detailed in Chapters 3.3 (line 888 ff. on page 25) and 3.4 (line 1052 ff. on page 29).
550	Federal Office of Consumer Protection and Food Safety (BVL)	DEU	Summary	Lines 49 to 53, page 2: The listing of areas of risk named under (1) to (6) is guided by Annex II of Directive 2001/18/EC. Sections 4.2 and 4.3 follow this structure. However, section 4.1 on genetically modified fish does not. It is desirable though to follow the structure as outlined in lines 49 to 53 throughout all respective sections wherever possible or to justify exceptions. Line 78, page 3: Editorial comment: “Therefore” should be deleted here.
551	GeneWatch UK	GBR	Glossary	Target organism requires a consistent definition throughout the Guidance (see comments in main text),
552	GeneWatch UK	GBR	References	Spielman, A. (2003) Release ratios employed for genetically modifying populations of mosquitoes In: Takken, W. & Scott, T.W., 2003. Volume 2 Ecological Aspects for Application of Genetically Modified Mosquitoes, Wageningen UR Frontis Series. Streicker DG, Recuenco S, Valderrama W, Benavides JG, Vargas I, Pacheco V, Condori1 REC, Montgomery J, Rupprecht CE, Rohani P and Altizer S (2012) Ecological and anthropogenic drivers of rabies exposure in vampire bats: implications for transmission and control. Proc. R. Soc. B doi:10.1098/rspb.2012.0538 Published online. http://rspb.royalsocietypublishing.org/content/early/2012/06/07/rspb.2012.0538 Tabachnick, W.J. et al., 1985. Oral Infection of Aedes Aegypti with Yellow Fever Virus: Geographic Variation and Genetic Considerations. The American Journal of Tropical Medicine and Hygiene, 34(6), pp.1219–1224. Thammapalo S, Nagao Y, Sakamoto W, Saengtharatip S, Tsujitani M, Nakamura Y, Coleman PG, Davies C (2008) Relationship between Transmission Intensity and Incidence of Dengue Hemorrhagic Fever in Thailand. PLoS Neglected Tropical Diseases 2(7): e263. doi:10.1371/journal.pntd.0000263 Thomé, R.C.A., Yang, H.M., Esteva, L. (2010). Optimal control of Aedes aegypti mosquitoes by the sterile insect technique and insecticide. Mathematical Biosciences 223, 12-23. Thresher, R (2008) Autocidal Technology for the Control of Invasive Fish. Fisheries, 33(3), 114-121. Van Den Hurk, A.F. et al., 2011. Vector Competence of Australian Mosquitoes for Yellow Fever Virus. The American Journal of Tropical Medicine and Hygiene, 85(3), pp.446–451. Walsh RK, Facchinelli L, Ramsey JM, Bond JG, Gould F (2011) Assessing the impact of density dependence in field populations of Aedes aegypti. Journal of Vector Ecology, 36 (2), 300–307. http://onlinelibrary.wiley.com/doi/10.1111/j.1948-7134.2011.00170.x/pdf Walsh RK, Bradley C, Apperson CS, Gould F (2012) An Experimental Field Study of Delayed Density Dependence in Natural Populations of Aedes albopictus. PLoS ONE 7(4): e35959. doi:10.1371/journal.pone.0035959. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0035959 Walters M, Morrison NI, Claus J, Tang G, Phillips CE, et al. (2012) Field Longevity of a Fluorescent Protein Marker in an Engineered Strain of the Pink Bollworm, Pectinophora gossypiella (Saunders). PLoS ONE 7(6): e38547. doi:10.1371/journal.pone.0038547. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0038547 White, S.M., Rohani, P. & Sait, S.M., 2010. Modelling pulsed releases for sterile insect techniques: fitness costs of sterile and transgenic males and the effects on mosquito dynamics. Journal of Applied Ecology, 47(6), pp.1329–1339

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553	GeneWatch UK	GBR	References	Ocampo, C.B. & Wesson, D.M., 2004. Population Dynamics of Aedes Aegypti from a Dengue Hyperendemic Urban Setting in Colombia. The American Journal of Tropical Medicine and Hygiene, 71(4), 506–513. Oxitec (2011a) Dilution of genetic traits. European Patent EP 1 624 749 B1. Grant of the patent 23.11.2011. Oxitec (2011b) Potential UK trial of “genetically sterile” (RIDL®) diamondback moth (Plutella xylostella). Powerpoint presentation to Health and Safety Executive (HSE) Scientific Advisory Committee on Genetic Modification (SACGM). Oxitec (2012) Oxitec Ltd. and Certis Europe B.V. Enter into Research Collaboration. Press Release. 13th January 2012. http://www.oxitec.com/press-release-oxitec-ltd-and-certis-europe-b-v-enter-into-research-collaboration/ PAT (2012) - Transgenic Aedes Project Progress Report – Feb 2011-Mar 2012. Patil, P. et al., 2012. Discussion on the proposed hypothetical risks in relation to open field release of a self-limiting transgenic Aedes aegypti mosquito strains to combat dengue. As. Pac. J. Mol. Biol. & Biotech., 18(2), pp.241–246. Phuc HK, Andreasen MH, Burton RS, Vass C, Epton MJ, et al. (2007) Late-acting dominant lethal genetic systems and mosquito control. BMC Biology 5: 11. doi:10.1186/1741-7007-5-1. http://www.biomedcentral.com/1741-7007/5/11 Poulter S, Bruce S (2010) As big supermarkets vow NEVER to sell clone meat or milk, the Mail tracks down the farmers with 96 more clone cows. Daily Mail. 5th August 2010. http://www.dailymail.co.uk/news/article-1300464/CLONING-Farmers-Steven-Callum-Innes-96-clone-cows-herd.html Reeves, R.G. et al., 2012. Scientific Standards and the Regulation of Genetically Modified Insects M. J. Lehane, ed. PLoS Neglected Tropical Diseases, 6(1), p.e1502. http://www.ploscollections.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0001502;jsessionid=C3DC4FD0650E395B0FD63D275A9703B5#pntd-0001502-g001 Reiter P, Amador MA, Anderson RA, Clark CG (1995) Short Report: Dispersal of Aedes aegypti in an urban area after blood feeding as demonstrated by rubidium-marked eggs. American Journal of Tropical Medicine and Hygiene. 52(2), 177-179. Robinson, A.S., Franz, G. & Atkinson, P.W., 2004. Insect transgenesis and its potential role in agriculture and human health. Insect Biochemistry and Molecular Biology, 34(2), 113–120. Sanders D, van Veen FJF (2012) Indirect commensalism promotes persistence of secondary consumer species Biol. Lett. rsbl20120572; published

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561	GeneWatch UK	GBR	5. Post-Market Environmental Monitoring plan	Line 6447: Environment and health risks must both be considered, not only of the GM animal but of its uses. Health risks must be monitored, especially for interventions involving disease vectors (James et al., 2011).
562	GeneWatch UK	GBR	4.3.9 Impact on human health	Lines 6381-6383: Not only direct exposure to the GM animal but also indirect risks must be included in the assessment and risk management must address these too. For example, if GM chickens act as a reservoir for infection as discussed in Section 4.3.3, there may be increased disease transmission in non-GM chickens and the human health risk may come from contact with the non-GM chickens. Similarly, if rabies from a GM animal were transferred to pets as described in Section 4.3.8, the risk to humans would arise indirectly via the pet not via contact with the GM animal.
563	GeneWatch UK	GBR	4.3.8 Impact on non-GM animal health and welfare	Line 6215: “If considered necessary” by whom?
564	GeneWatch UK	GBR	4.3.5 Interactions of the GM mammals and birds with non-target organisms	Line 5965: GM animals that mate with wild animals and fail to reproduce, or produce offspring with reduced fitness, can also have devastating effects on the wild population and non-target organisms c.f. the ‘sterile’ rabbit example or similar population suppression approaches i.e. limiting reproduction is not always a measure to reduce harm. GM animals may also exhibit “conditional lethality” (see GM insects section): otherwise how will they be reproduced in the laboratory? Can the mechanism by with they are produced in the lab also occur in the wild? If so, under what circumstances? What is the penetrance of the ‘sterility’ trait i.e. no offspring or just a reduced number? Are there also aborted foetuses, stillbirths, deformed offspring? If so, what are the impacts of this (including on animal welfare and the environment)? Lines 5993-5994: Reducing persistence and invasiveness does NOT necessarily reduce indirect risks: see comments on line 5965: population suppression approaches can have major impacts on ecosystems. If approved, how will releases be restricted to specific receiving environments? For example, the GM ‘sterile’ rabbit would presumably not be released in Spain, where the European rabbit is endangered and rabbits are the main diet of the endangered Lynx. Were GM ‘sterile’ rabbits considered suitable for authorisation for release elsewhere in the EU, how would their receiving environments be restricted? Would there be penalties for individuals taking rabbits from one part of the EU to another unless they could certify that they were not GM?

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565	GeneWatch UK	GBR	4.3.5 Interactions of the GM mammals and birds with non-target organisms	Lines 5559-5563: As noted above, due to definition of target organism used in this section, there is no section of the guidance dealing with the impacts of population suppression approaches for pests on the pest population. This needs to be considered first, then extended to the interactions with NTOs. For example, the release of 'sterile' GM rabbits may or may not succeed in reducing the target population of rabbits and there could be fluctuations in time or increases in rabbits in the surrounding area, and changes in the rabbit population structure (more males, less young etc.). Once the population dynamics of these aspects (i.e. interaction between the GM pest and the non-GM pest) are understood, it is the possible to look at interactions with NTOs i.e. predators, competitors and prey. It is not only loss of an endangered prey species that needs to be considered: for example, there could be an increase in a competitor, which might have adverse consequences if it is a pest. Further, there will be feedbacks between the population dynamics of the different species: for example, population suppression of the target pest might be successful initially but reduce a food source for predators, resulting in a loss of predators followed by a rebound in pests. See the extensive comments on the population suppression approach in the GM insects section. Whilst this omission is most obvious for population suppression approaches (which are intended to reduce or eliminate the wild population) it should also be considered here whether any loss of fitness in any GM mammal or bird could impact on wild populations, following mating and poor survival of the offspring. For example, if a sterility (or partial-sterility) trait were introduced into a GM chicken with the aim of reducing the risks of persistence or invasiveness should it escape an intensive production system, what would happen if such chickens were inadvertently introduced into free-range chicken farms? Lines 5599-5609: Competitor species should not be forgotten. Line 5616: It is confusing to have non-GM individuals of the same species described as non-target organisms here, when they are regarded as target organisms in the insects section. Also, population dynamics of non-GM individuals of the same species needs to be considered more thoroughly than it is here, see comments on lines 5559-5563. Lines 5656-5671: The population suppression approach needs to be considered more carefully here (i.e. the 'sterile' rabbit example, but bearing other invasive species in mind e.g. rats). Lines 5698-5699: Increases in harmful competitor pest species, disease vectors or predators as a result of the introduction of the GM animal also need to be considered: these may then have a secondary effect on a vulnerable species or on pathogens or humans. Lines 5775-5776: Different effects may occur at different life stages. Lines 5841-5841: It is not just question of data but also adequate understanding of a complex, dynamic system: this includes the need for theoretical concepts that adequately describe the necessary ecosystem processes.
566	GeneWatch UK	GBR	4.3.4 Interactions of the GM mammals and birds with target organisms	Lines 5365-5370: This definition of target organism is extremely confusing, see comments on lines 1832-1843. A better approach would be to define the target organism as the species that is being genetically modified (as is done in the insects section). Whilst the issues included here are important they could be included in Section 4.3.3. An entirely new section is needed to address the impact of releases of the GM on the population dynamics of the wild species (compare Section 4.2.3 for insects and comments above on this section). This is particularly important for the 'sterile' rabbit or other population suppression approaches (e.g. 'sterile' rats) but also for any application with altered fitness which may change the population dynamics of the wild species (and hence of other species as discussed in Section 4.3.5).

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567	GeneWatch UK	GBR	4.3.3 Pathogens, infections and diseases	Line 5033: It is confusing for the reader to see some of the information on pathogens deferred to Section 4.3.4, due to the conflicting definitions of "target organism" used in the document (see comments on lines 1832-1843). In addition, there is insufficient attention paid to the possible hazards of the population suppression approach (as represented by the 'sterile' rabbit). This type of approach might conceivably be applied with a view to reducing transmission of diseases (including those that might be transferred from animals to humans). However, this requires a full understanding of how this form of culling (reduction of the population through inherited forms of sterility or loss of fitness) might affect disease transmission. Such effects can be counter-intuitive leading to increased disease where a reduction was expected. For example, a recent study of the effect of culling bats on rabies transmission in Peru found that the prevalence of the virus was not reduced by culling and that the programme may even have been counter-productive (Streicher et al., 2012). This study confirms other findings in badgers and bats that suggest culling in wildlife disease systems can sometimes increase disease prevalence when it stimulates the recruitment of susceptible individuals or increases host dispersal. Theoretical modelling of a population of game has shown that culling can increase disease prevalence in animals and mortality (Choisy & Rohani, 2006). Lines 5134-5140: This paragraph does not seem to adequately reflect the variety of hazards identified below e.g. evolution of viruses, compromised immunity etc. Lines 5201-5212: Suggested additional reference: Greger (2011). Line 5231: reference Velthuis et al. (2007) is missing from the reference list. Lines 5294-5334: Reference should be made throughout this section to the need to validate computer models and the need for a variety of alternative conceptual models to be developed to ensure that worst-case scenarios are captured. Line 5344: If a particular farm must produce only GM animals in order to mitigate risks this reinforces the need for traceability (see line 4439) and mechanisms for the enforcement of any authorisation conditions.
568	GeneWatch UK	GBR	4.3.2 Vertical and horizontal gene transfer	Lines 4787-4884: As noted in comments on line 4446, the hazards associated with vertical gene transfer of 'sterility' traits or similar (i.e. population suppression approaches) have been completely omitted here. This problem is compounded by the different definition on "target organism" being used for mammals and birds compared to insects (see comments on lines 1832-1843). If the same definition is used in this section as for insects then impacts on population dynamics of the wild species could be included in the "target species" section (see Section 4.2.3 and comments on this above). Line 4806: Reference EFSA (2011e) is missing from the reference list. Line 4811: What about genes that are unadvantageous e.g. sterility but also any loss of fitness? Vertical gene transfer from the GMO to the wild species could then harm that species. See comments on population suppression approaches throughout this document. Line 5031: EFSA (2009g) is missing from the reference list.

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569	GeneWatch UK	GBR	4.3.1 Persistence and invasiveness of GM mammals and birds and vertical gene transfer to wild and feral relatives	Line 4446: The title of this section is confusing: it implies vertical gene transfer to wild relatives is included, but only covers issues of persistence and invasiveness. It is then very unclear to the reader what aspects of vertical gene transfer are included in Section 4.3.2. However, the theoretical 'sterile' rabbit application is intended to crash the wild population of this species and could also have unintended consequences for whole ecosystems. It achieves this through the opposite of being persistent: it is engineered to mate with the wild population and cause that population to die out (through vertical gene transfer of the sterility trait). Issues associated with population suppression approaches such as this have in general been treated poorly throughout the Guidance (see comments on fish and insects) and a consistent approach is needed to capture these risks. Line 4451: Remedial action may not reverse damage. Line 4468: Keller et al. (2011) is not in the reference list. Line 4621: Wheeler et al. (2001) is not in the reference list. Line 4634: Shears et al. (1991) is not in the reference list. Is this also relevant to the fish section? Line 4753-4755: The recommendation that sterile releases should always be considered has not been properly thought through: the theoretical 'sterile' rabbit application is intended to crash the wild population of this species and could also have unintended consequences for whole ecosystems. Whilst sterility may minimise the issues of concern considered in this section (i.e. invasiveness and persistence) it can exacerbate other concerns through its potential impact on wild populations and ecosystems. In particular, any GM animal that mates with wild animals can be regarded as having close contact with the wild species and a potentially large impact on it, whether the offspring survive or not: greater fitness in the offspring means more potential for persistence and invasiveness, but reduced fitness (or sterility) means more potential to suppress or even wipe-out the wild population, with potentially significant effects on other species due to interactions.
570	GeneWatch UK	GBR	4.3 Specific areas of risk for the ERA of GM mammals and birds	Line 4439: Escape is important but so is human error or ignorance of regulations or failure to follow them. For example, GM chickens authorised for contained use in intensive production might still be sold to free-range chicken farmers, or smuggled out of factories etc. Traceability will be important for all species as e.g. eggs, sperm, embryos and adults (e.g. a male sire). For example, cloned cattle were exported to Scotland as embryos, and ended up in the food chain (Poulter & Bruce, 2012).
571	GeneWatch UK	GBR	4.3 Specific areas of risk for the ERA of GM mammals and birds	Lines 4370-4409: The scope of the Guidance should be clarified: see comments on Line 266: why is the use of GM animals for production of pharmaceuticals excluded from ERA? Transgenic goats that produce ATryn (an antithrombin drug for human therapeutic use) in their milk already exist on a farm in Massachusetts: ATryn was authorised for use in the EU in 2006 and in the US in 2009; applications involving the production of other pharmaceuticals in the milk of cattle, sheep and goats and the production of recombinant protein in birds eggs are being developed (FERA, 2010). The deliberate release of any of these GM animals in the EU should require an ERA. Further, the guidance should state more specifically which traits count as "production of pharmaceuticals" (lines 30, 226 and 596) for the purposes of this guidance. For example, are cows (or other animals e.g. sheep, goats, pigs, rabbits) genetically engineered to produce low-lactose or high-omega-3 milk or human proteins such as lysozyme or lactoferrin in milk included or not (Yang et al., 2011; Gray, 2012; FERA, 2010; Anon, 2012b)? Where is the line drawn between nutraceuticals and pharmaceuticals? If these applications are to be included, re-consultation is necessary so that consultees know what they are being consulted about. Presumably production of high omega-3 meat in transgenic pigs (Lai et al., 2006) is included in the remit of the Guidance, but it is odd that this application is not discussed. In general, the rationale for the choice of GM animal and bird examples is very unclear. The so-called Enviropigs at the University of Guelph were ordered to be destroyed in April 2012 (Nickel, 2012): it seems unnecessary to waste time on them. US company Exemplar Genetics aims to sell GM pig models for use in academic and pharmaceutical laboratories and there are concerns these might enter the food chain accidentally (Maxmen, 2012), but it is not clear whether these animals fall within the scope of this draft guidance. Would there really be a market in the EU for an enhanced growth cat (given both the environmental concerns and ethical and animal welfare issues especially surrounding the production process) and is any such product really being developed? Is it really the case that the release of GM 'sterile' rabbits "can be forseen in the near future"? None of the references in FERA (2010) suggest that such an application is close to being developed and it is unclear how sufficient numbers could be released for a population suppression application unless the sterility trait is somehow conditional (allowing breeding in the lab): more information is needed to allow informed comment. And if rabbits, why not other species, e.g. rats, grey squirrels? Rabbits as bioreactors producing bioactive chemicals in their milk are highlighted in the FERA report (FERA, 2010) and the Dutch company Pharming is now focusing on protein production in transgenic rabbits (Anon, 2012b), but these

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				applications are not discussed, and nor is the escape of transgenic lab rats, although this issue was highlighted in page 32 of the expert report (FERA, 2010). The “avian flu resistant chicken” is at the proof-of-concept stage and impacts and disease transmission are as yet unknown (see discussion in Section 4.3.3).
572	GeneWatch UK	GBR	Step 6: Overall risk evaluation and conclusions	Lines 4364-4366: Particular attention should be paid to risks to the health of individuals living in disease-endemic areas, due to adverse impacts on disease transmission (by target or non-target species), evolution of viruses, or impacts on immunity or cross-immunity. Experiments with disease vectors require informed consent and should not be conducted until these risks have been assessed.
573	GeneWatch UK	GBR	Step 4: Risk characterisation	Lines 4348-4362: Perhaps the principle “first, do no harm” should be recalled at this point. Again, everything is focused on direct exposure, although indirect effects could cause significant harm by e.g. increasing transmission of diseases. Virus evolution is also missing. This section should be rewritten and re-consulted on.
574	GeneWatch UK	GBR	Step 4: Risk characterisation	Lines 4333-4346: see comments on lines 4301-4346. Also: where is the discussion of receiving environment (including for example, which vectors are present there)? This is of critical importance because of the possibility of establishing new vectors in areas where they don’t currently exist (this might be the target vector or a non-target vector).
575	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 4301-4346: This section does not consider any of the indirect hazards described above (i.e. hazards which come not from contact with the GMO but from the effect of releases on target and non-target species). The reader is inclined to feel that all input to the above sections on impacts on target and non-target species have been a waste of time as these effects are then totally ignored when it comes to the important endpoint of impacts on human health. Line 4326: Risk of escape is also important.
576	GeneWatch UK	GBR	Step 2: Hazard characterisation	Line 4232: This section needs to be amended to take account of the comments above. The possible increase of other (non-target) disease vectors is a particularly important omission. Line 4259: Strains are important, not just species. Viruses may evolve in response to altered properties of GM insects (Medlock et al. 2009): it is not clear how it is proposed this issue should be dealt with in the ERA. Line 4265: Delete “might”, replace with “should”. Line 4267: Delete “In case a replacement strategy is proposed”: it is important to test vector competence for population suppression approaches also, as lethality is partial, conditional etc. and there will be some introgression of traits into the wild population. Line 4286: This sentence is not about “SIT” it is about populations suppression using GM insects. Development of resistance, loss of fitness etc. must be considered. Line 4290: A new section on health hazards due to increases in non-target disease vectors must be added. Lines 4291-4295: Modelling alone is insufficient and models must include all relevant effects or they are useless (see comments on lines 4420-4227). Models should be developed and validated so that they represent real-world effects in the absence of releases first (a step-by-step approach). Releases in endemic areas where human immunity plays an important role should only be considered as the final step in a step-by-step approach as required by the Directive (EC, 2001). Cross-immunity as well as loss of immunity must be considered. Other problems with suppression must also be considered e.g. potential to increase disease vectors in surrounding areas, fluctuations in populations as a result of interactive effects (see comments on impacts on target and non-target organisms above). Loss of efficacy of populations suppression must also be considered as well as loss of efficacy of other traits in the population replacement approach (e.g. if disease transmission properties are reduced, will these be maintained?). There must be baseline monitoring of health and antibodies etc. before any open releases. Impacts of releases on disease must be evaluated following appropriate protocols (James et al., 2011).

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577	GeneWatch UK	GBR	4.2.6 Impact on Human Health	Lines 4420-4227: This section needs to recognise that temporary or partial efficacy in terms of population suppression can harm: it is not simply a question of changing human behaviour. For example, a rebound in cases of disease can occur (Curtis et al., 2003; Scott & Morrison, 2003; Egger et al., 2008). If population suppression is ineffective it may have no impact on disease transmission (if transmission thresholds are low) and it is also possible that mosquito populations increase in areas neighbouring the release site. Further, long-term suppression may fail due to effects discussed above such as loss of fitness or development of resistance. Cross-immunity as well as immunity may be important: for example, Oxitec's models of dengue transmission (Yakob et al., 2008; Alphey et al., 2011b) omit the important effects of cross-immunity between multiple serotypes of dengue fever on the incidence of dengue haemorrhagic fever and thus assume that only beneficial impacts on disease impacts can occur, when in practice there could be significant harm if population suppression in high-transmission areas is only partially effective (Thammapalo et al., 2008; Nagao & Koelle, 2008; GeneWatch UK, 2012). The most serious and often fatal form of dengue, dengue hemorrhagic fever (DHF), appears to be more likely when a person is infected by a second serotype of dengue fever, having already been infected by one of the other serotypes. This is thought to be due to immunological mechanisms including antibody dependent enhancement (ADE), in which the antibodies developed against the first infection make the second infection more severe. However, if the two infections with different serotypes occur in quick succession (within weeks) cross-immunity can develop which has the opposite effect, reducing the risk of DHF. Many of the individuals in areas of high vector mosquito abundance would be infected by, and acquire immunity against, multiple serotypes while they are protected by this cross-immunity and develop resistance to DHF unknowingly. One concern about partially effective interventions to reduce mosquito numbers is that as the mosquito abundance decreases, an increasing number of individuals would experience secondary infections after the protective cross-immunity has waned, and the incidence of DHF would then increase. One study in Thailand has suggested that in regions of intense transmission, insufficient reduction of mosquito populations may increase long-term incidence of DHF, because of the existence of this complex cross-immunity effect. This analysis suggested that reducing Aedes aegypti abundance from the highest level in Thailand to a moderate level would increase the incidence of DHF by more than 40%. Further computer modelling of this data has confirmed this finding. If correct, this has major implications for dengue control programmes, including the use of Oxitec's GM mosquitoes. It suggests that ineffective programmes may be worse than useless because they can actually increase the harm due to the disease, at least in high risk areas.
578	GeneWatch UK	GBR	4.2.6 Impact on Human Health	Line 4165: The wording in the Directive (EC, 2001) is coming into contact with or in the vicinity of the GM release(s). The rewording given here implies that it is only direct health impacts (e.g. from being bitten by the GM insect) that are important. In the case of population suppression approaches adverse health impacts can also occur indirectly, especially via: (1) the impacts of the GM releases on the non-GM target species (e.g. due to poor or temporary efficacy, rebounds in numbers, increases in the area surrounding the release site); (2) the impacts of population suppression on other disease vector species, especially increases in competitor disease vectors (see comments above and GeneWatch UK, 2012). These issues are largely ignored here in favour of issues relating to direct contact only. For disease prevention applications, the ultimate endpoint is disease incidence and severity (James et al., 2011): it is important that this is assessed because (i) population suppression may not be effective (or may be only temporary); and (ii) successful population suppression does not necessarily mean less, or less severe, disease, due to issues such as disease transmission thresholds and human immunity and cross-immunity (see comments on lines 4220-4227). It is important that informed consent is obtained for studies involving disease vectors. Lines 4166-4168: The ingestion route will be important, especially for GM agricultural pests, and has been completely ignored and excluded from any consultation process (see comments on lines 267-272). Line 4182: Toxicity testing should be required for all exposure routes (e.g. ingestion, biting): the introduction of toxic proteins could clearly have adverse impacts on human health and could be introduced via bites (e.g. mosquitoes or ticks) as well as ingestion or inhalation. Line 4192: Allergenicity must be assessed for all exposure routes. Lines 4203-4204: Changes to population structure e.g. age, size can also affect disease transmission. Strains must be tested and non-native strains must be avoided: otherwise there is potential to introduce enhanced transmission via new strains of disease vectors e.g. for Yellow Fever when trying to tackle dengue (GeneWatch UK, 2012). Lines 4218-4219: Development of resistance, loss of fitness etc. need to be considered here. Contamination of production facilities with pathogens must also be considered. The potential for a different species of disease vector to increase or become established as a result of population suppression is of recognised importance and must be included in this section (Beech et al., 2009; GeneWatch UK, 2012). This is because GM approaches are species-specific, unlike many other approaches (e.g. removing breeding sites, or using traps or larvicides).

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				Line 4205: Possible evolution of pathogens in response to GM insect releases needs to be considered (e.g. Medlock et al.2009).
579	GeneWatch UK	GBR	Step 5: Risk management strategies	Line 4137: It is not clear what is meant by "compared to non-GM related outcomes" (especially when there may be other GMOs in the environment e.g. GM insects combined with GM crops): this phrase should be deleted. Line 4154: An entire section i.e. Impact on animal health has been omitted here. Insects transmit many pathogens to animals, via many routes e.g. ingestion, biting, transfer of pathogens from faeces to food. Proposed applications might in future include GM ticks or midges, with a view to reducing the impacts of animal diseases. The relevant issues need to be considered in detail. A new section therefore needs to be added here and then consulted on. This should build on the proposed new pathogens section (see comments on line 3677). Issues discussed below that are relevant to human health (e.g. impacts on immunity, increase in alternative vectors or disease transmission routes, evolution of viruses) may also be relevant to animals.
580	GeneWatch UK	GBR	Step 4: Risk characterisation	Lines: 4131-4133: Multiple receiving environments and management practices must be considered. Changes over time must be considered e.g. taking into account loss of efficacy might (e.g. due to development or resistance, loss of fitness). The focus should be on risks, this Guidance is for risk assessment (see comments on lines 4092-4094), this section is about risk characterisation.
581	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 4114-4115: Short-term and long-term changes must be considered e.g in response to the development of resistance. Lines 4121-4125: It is not correct to state that these models have been validated.
582	GeneWatch UK	GBR	Step 2: Hazard characterisation	Lines 4099-4101: Multiple management systems need be considered, including changes over the short- and long-term. Line 4106: Alternative conceptual models must be explored in order to identify worst-case scenarios and models must be validated.
583	GeneWatch UK	GBR	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Lines 4063-4080: Need to add here: changes in management system (e.g. suspension in use of larvicides, adulticides or public health approaches to removing breeding sites) may be needed during a GM insect release programme but changes to these measures could reduce controls on other GM disease vectors or GM pests. Continued use of control measures such as insecticides during release programmes could affect population dynamics in complex ways: impacts on efficacy and safety of the programme therefore need to be considered (Thomé et al., 2010). Lines 4081: Should include protection of human health. Lines 4092-4094: The sentence "Alteration to management practices might provide both environmental benefits as well as harm so that the net environmental impact of the overall production system needs to be considered" must be deleted. EFSA's Guidance on the environmental risk assessment of genetically modified plants (EFSA, 2010a) states clearly: "The overall risk/benefit is out of the remit of the EFSA mandate. The ERA should primarily focus on potential environmental risks arising from the GM plants". The sentence added here (presumably inserted at the request of Oxitec/Syngenta) is not consistent with EFSA's mandate and is a blatant attempt to change EFSA's mandate and the entire purpose of the ERA process through the back door. The addition of this sentence raises a number of serious concerns: (1) The Guidance is intended to assist applicants to produce an environmental risk assessment as defined in Article 2, paragraph 8 of Directive 2001/18/EC (EC, 2001), this does not include an assessment of potential benefits; (2) this proposal amounts to a significant proposed change in the purpose and role of environmental risk assessment, which should not be buried on page 97 of a draft Guidance document; (3) EFSA has no competence to assess claimed environmental benefit: its remit is safety of the food chain (EC, 2002); (4) net environmental impact will be context-specific (i.e. depend on the ecosystem at the target site and a wide range of alternative management practices) and vary with time (e.g. as resistance develops): it is therefore unlikely that claimed benefit can be quantified in a manner that is meaningful in the context of the single market; (5) claimed benefits are likely to be contentious and disputed: if environmental net benefit were to be assessed, relevant guidance and jurisdiction over such assessments would need to be developed and an appropriate body would need to be allocated this task; (6) programmes for large-scale releases of GM insects for pest control or public health purposes may well be subject to a Strategic Environmental Assessment (SEA) under EC Directive 2001/42/EC, however the role of the EC in evaluating net environmental impact at an individual farm level is less clear: even where an SEA is required, this does not replace the legal obligation to conduct an ERA consistent with the requirements of 2001/18/EC.

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584	GeneWatch UK	GBR	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Line 4062: It should be recognised here that management systems are likely to change with time e.g. as resistance develops to the GM trait, ecosystems change (e.g. in response to the GM releases or to climate change) and new technologies are developed (e.g. new larvicides or mosquito traps, better disease interventions such as vaccines) or farming practices change. Multiple GM insects might be introduced into the same management system in future. For example, Oxitec has responded to concerns that the dengue-transmitting species of mosquito Aedes albopictus might increase in response to its releases of GM Aedes aegypti by saying that it could introduce a GM Aedes albopictus population suppression programme (presumably based on its prototype flightless-female technology) in combination with a GM Aedes aegypti release programme (Alphey et al., 2010). A major proposed application is to combine GM agricultural pests with GM crops (pest-resistant Bt crops) in an attempt to tackle the growing problem of the emergence and spread of resistant pests (Alphey et al., 2007; Alphey et al. 2009; Oxitec, 2011b): discussion of the implications of this strategy should have been included in this draft Guidance document. One proposal, for example is to reduce the size of non-Bt-crop refuges and use GM insect releases to slow resistance instead: this clearly has implications that should have been discussed. Again, long-term risks must be considered (e.g. potential increased use of more hazardous pesticides when neither the Bt plant nor the GM crop is any longer effective, due to development of resistance in both systems). If a non-target pest increased (as has been observed e.g. in association with Bt cotton in China : Zhao et al., 2011), would a different species of GM insect then be introduced to tackle that? How would the complexity of this system be addressed? Presumably more than one company could become active in this area in future: therefore the possibility of multiple applications being released or escaping into the same receiving environment also needs to be considered. Other potential applications that have not been discussed include the possible development of pesticide-resistant bees or other beneficial or useful insects (e.g. silkworms): such applications might result in increased use of pesticides.
585	GeneWatch UK	GBR	4.2.5 Environmental impact of the specific techniques used for the management of GM insects	Line 4054: There will not be one “comparable non-GM insect system” but many, because there are a wide variety of ecosystems in the EU and also multiple approaches to tackling pests, e.g. for agricultural pests agro-ecological systems versus more intensive systems, large-scale and small-scale farming systems, open fields, polytunnels and greenhouses, monocultures etc. etc. The same is true for disease vectors, see comments on lines 2949-2950. Management practices and any changes to them will be context-specific (i.e. depend on the ecosystem at the target site and a wide range of alternative management practices) and vary with time (e.g. as resistance develops, or as new tools become available e.g. vaccines or better monitoring for diseases). This likely diversity of management systems is recognised in EFSA’s Guidance on the environmental risk assessment of genetically modified plants (EFSA, 2010a) which states that the ERA shall: describe the potential range of GM-based management and production systems likely to occur across receiving environments and how they differ from current management systems; identify the potential adverse environmental impacts associated with these systems; assess to what extent the environmental impacts overlap those of the range of non-GM systems; determine which conditions (receiving environments, management and production systems) are related to potential higher adverse effects than current systems; assess to what extent the range of GM management and production systems would meet the assessment endpoints identified in the other chapters. Similar wording should be used here. Management regimes are likely to be complex: for example, Oxitec and co-authors state: “our analysis leads us to conclude that in many instances the optimal strategy is likely to be an IVM [Integrated Vector Management] program with a significant SIT [Sterile Insect Technique] component but also using other methods, especially insecticides” (Alphey et al., 2010).
586	GeneWatch UK	GBR	Step 6: Overall risk evaluation and conclusions	Lines 4035-4044: The concept of assessing feedback between effects on non-target organisms and effects on target organisms is missing here e.g. a reduction in target organism might lead to a reduction in predators which might lead to a rebound in numbers of the target organism. For example, for a population suppression approach, this could have adverse effects on the intended endpoints e.g. crop damage or human health. NTOs can have direct, indirect and multitrophic effects with GM animals, see Section 4.3.5 (in GM mammals and birds) and e.g. Figure 9. It is difficult for the reader to understand why such effects are discussed in detail for mammals and birds (where current proposed applications are mainly semi-contained) but ignored for insects (where proposed applications will involve large-scale open releases). Line 4044: An entirely new section must be added here on pathogens, infections and diseases, to parallel subsection 4.1.4 for GM fish. See comments on line 3677.

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587	GeneWatch UK	GBR	Step 5: Risk management strategies	Lines 4020-4021: The comment regarding receiving environments is important: for example, a GM species-specific approach might be approved for an area where the crop or disease is eaten or spread by only one pest or vector, but not approved where there is more than one pest or vector, due to concerns about potential increases in these species. However, the issue of how spread of GM eggs, larvae and adults into unapproved receiving environments requires a lot more thought than is given here: see comments on lines: 3627-3629. Lines 4024-4025: The sentence “This is of particular importance when applying replacement strategies” should be deleted. Line 4028: Mitigation might also be needed for non-target species not just the GM insect, e.g. to tackle an increase in a non-target pest. Lines: 4032-4033; A step-by-step approach to is also important in minimising risks. See comments on lines 248-250.
588	GeneWatch UK	GBR	Step 4: Risk characterisation	Lines 3977-3978: Not just risks caused to NTOs, risks caused by interactions with NTOs, including e.g. increases in non-target pests or disease vectors. Implications for crop damage need to be considered here and implications for human and animal health in future sections (a subsection on animal health is missing and needs to be included). Lines: 4002-4003: It may be impossible to reverse adverse effects even if the released GM insect population can be eradicated (e.g. if an invasive competitor has become established)
589	GeneWatch UK	GBR	Step 3: Exposure characterisation	Line 3944: The term “exposure pathways which may harm the environment” is too narrow. “Exposure pathways” implies direct toxicological effects (excluding, for example, increases in competitor species) and human health should also be included here (for example, an increase in a competitor disease vector may harm human health). Line 3945: Not only adverse effects on NTOs, also increases in harmful NTOs. Lines 3948-3953: Release ratios are also needed. Note: the structure of the Guidance risks being repetitive here: all these parameters are also needed to assess the effects on target organisms too. There should be a better way to organise this information. Line 3968: The RIDL population replacement strategy involves repeated large scale releases for decades. Hence the sentence claiming that climatic changes are of particular importance for replacement strategies should be deleted. Line 3970: Should refer not just to the GM insect but to competitors, prey, hosts, symbionts, predators etc. as this is what this section is supposed to be about and their ranges can also change with climate. The same is true of pathogens but a whole new section needs to be added to deal with these, as noted above.
590	GeneWatch UK	GBR	Step 2: Hazard characterisation	Lines 3854-3855: The concept of environmental endpoints that “need to be protected from harm” is too restrictive as it ignores the possibility of increases in harmful competitor species. Lines 3867-3870: Pest regulation is critical and needs to be properly quantified, not ignored as “too difficult”. If it is too difficult a precautionary approach means that releases should not be allowed. Lines 3871: Restriction to “potential hazard to NTOs” is too restrictive a definition: it does not encompass potential increases in harmful non-target species (e.g. pests or disease vectors, which might then cause damage to crops, endangered species or human health). Line 3873: The strain as well as the species is important. Lines 3892-3896: Population dynamics of the target and non-target species and their interactions (e.g. larval competition) must be understood, otherwise risks such as increase of non-target pests due to competitive displacement cannot be assessed. Information on ability of species to recover is important, but so is information on the ability of competitor disease or pest species to persist. Line 3889: Not just “hazards for non-target species”, also potential increases in non-target disease vectors or pests.

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			Line 3900: Properties of the strain e.g. disease transmission must also be measured. Line 3909: It is not correct to say that susceptibility to pesticides (and disease transmission properties) are mainly relevant for replacement strategies as there may be introgression into wild relatives in population replacement strategies and the GM insects may also survive as a result of incomplete penetrance, failed conditionality, resistance etc. Line 3913: Distribution of competitors is also important (as this relates to potential increase in non-target pests or disease vectors). Line 3923: Delete the word “especially”: some issues, e.g. increases in competitors, are more likely to be a problem with population suppression approaches. Line 3926: The word “sterile” is misleading: this should refer to partial, conditional, late-acting lethality. The reference to adult-only life stages is misleading: see comments on lines 3843-3845. (This is an especially problematic claim for female-killing approaches). Line 3929-3933: “Sterile” is misleading. This whole section is again confused about whether open experimental releases can be made or not. Reference should be made to the step-by-step approach required by the Directive (EC, 2001), see comments on lines 248-250. For example, surveys of competitor species and studies of inter-species competition can be made in the undisturbed proposed release environment (wild target and wild non-target species) and in the lab and caged trials (GM target, wild target and wild non-target) and can be combined with modelling approaches to seek to predict likely effects of competitive displacement. Applications for open release experiments should only follow if these earlier studies suggest that such releases will not to lead to an increase in harmful competitors and if it has been established that releases will not spread to other environments where such effects might pose a problem. Line 3934: Replace “can” with “should”. Lines 3937-3941: This paragraph must include competitor species and methods to establish that harmful competitor species will not increase or become established in new areas.

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591	GeneWatch UK	GBR	4.2.4 Interactions of the GM insect with non-target organisms	Lines 3819-3820: The ERA is required to take into account GMOs already in the environment (EC, 2001, Annex II). This might include other GM insects, GM crops or GM fish, mammals or birds. Multiple GM insect species may be released where there is more than one disease vector or agricultural pest. For example, Oxitec has responded to concerns that the dengue-transmitting species of mosquito Aedes albopictus might increase in response to its releases of GM Aedes aegypti by saying that it could introduce a GM Aedes albopictus population suppression programme (presumably based on its prototype flightless-female technology) in combination with a GM Aedes aegypti release programme (Alphey et al., 2010). A major proposed application is to combine GM agricultural pests with GM crops (pest-resistant Bt crops) in an attempt to tackle the growing problem of the emergence and spread of resistant pests (Alphey et al., 2007; Alphey et al. 2009; Oxitec, 2011b). If a non-target pest increased (as has been observed e.g. in association with Bt cotton in China : Zhao et al., 2011), a different species of GM insect might presumably then be introduced to tackle that. Line 3826: See comments on “temporary”, lines 3724-3725. Lines 3831-3835: This discussion of receiving environments is extremely poor, see e.g. comments on lines 3565-3568. Issues to be considered include: (1) density of target species (presence or absence, likely efficacy of suppression etc.); (2) other species e.g. presence or risk of introduction of competitor pest or disease vector species; (3) human habitation. Implying that human-made habitats are lower risk is completely wrong: for example human immunity effects can create increased risks to human health if population suppression approaches to disease vectors are used in inhabited areas where disease transmission is high (see e.g. GeneWatch UK, 2012 and comments on Section 4.2.6). Lines 3836-3842: This paragraph ignores the risks of introducing non-native GM species and strains to areas where they are not currently established. Lines 3843-3845: It is not correct to state that some GM insects will only be present at specific life stages: for example Oxitec’s GM insects mostly die at the larval stage but some survive to adulthood and large numbers of adults will be continually released (including a small percentage but potentially large number of females due to imperfect sorting). Female-killing approaches will also obviously allow multiple generations of males to survive in the environment.
592	GeneWatch UK	GBR	4.2.4 Interactions of the GM insect with non-target organisms	Line 3725: It is difficult to understand why this sentence is restricted to “natural enemies” when the Directive (as cited in line 3678) is clear that many other species and interactions must be considered e.g. competitors. The argument that short-term presence of the GM insects cannot lead to long-term effects is incorrect: for example, if an invasive competitor where to become established due to competitive replacement whilst the population of the target organism is suppressed this effect might not be reversible. Similarly, if it were true that the target pest is likely to be eradicated, this could have irreversible effects (including other extinctions). Effects on competitors are very important because many diseases are spread by more than one vector and many crops have more than one pest. If the ecological niches of these species overlap, i.e. if they are competitors, the use of the population suppression approach (which is species-specific) could lead to increases in competitors with potentially harmful (and possibly irreversible effects). Although this is discussed in lines 3739-3756, this is not reflected in this paragraph, which downplays the risks and implies all such effects would be reversible. Line 3769: However, indirect effects of the population suppression approach on pollinators should be considered. Line 3775: Should refer to potential increases in competitors. Line 3783: See comments on “limited in space and time”, lines 3724-3725. Lines 3786-3787: See comments on “preventative releases”, lines 3565-3568. Lines 3788-3790: Suppression of a non-native species can still have significant effects on biodiversity, e.g. if numbers of another non-native species increase. Lines 3791-3804: It is unclear why a separate section on biogeochemical processes and abiotic interactions has not been included, to parallel the requirements of the Directive in Section D.1 of Annex 2 (point 8) (EC, 2001). This would aid consistency within the Guidance i.e. with GM fish and GM mammals and birds (Subsections 4.1.5 and 4.3.6), both of which extend to several pages. The numbers of dead larvae and pupae introduced

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				into the environment if Oxitec's RIDL technique is used commercially will number many millions per week (e.g. PAT, 2012 reports scaling up production to 2.5 million GM male mosquitoes a week: although perhaps only 10% of these will mate successfully each female lays multiple eggs which are expected to hatch and die at the late-larval stage). Large numbers of dead female adults may also arise from some female-specific approaches such as flightless female Aedes albopictus mosquitoes (Labbé et al., 2012). Dead GM insect larvae, pupae or adults (whether disease vectors or agricultural pests) might have effects on e.g. water quality or soils. Some insects can lay very large numbers of eggs. Applicants should estimate the number of dead larvae etc. likely to enter the environment as a result of the proposed release programme and quantify their expected fate (e.g. percentage eaten by predators, rotting on the ground, in fruit or vegetables, or in water supplies etc.).
593	GeneWatch UK	GBR	4.2.4 Interactions of the GM insect with non-target organisms	Lines 3699-3703: Impacts on animal health must also be considered, see proposal for a new section on this (comment on line 4154). Why are impacts on crops also completely omitted? For releases of GM agricultural pests a key endpoint will be crop damage: this must be considered both in terms of efficacy (i.e. whether the releases are achieving their intended purpose of reducing crop damage) and in terms of unintended consequences. For example, the GM releases might allow plant pests to become established in new areas and increase crop damage: for example, this might be either be through the GM insects or hybrids becoming established and directly causing damage, or through competition effects allowing new plant pests to be established. See also comments on plant pathogens (comments on line 3677).Compliance with plant pest legislation will be essential. Line 3719: Oxitec envisages continued releases of its GM mosquitoes for more than 50 years (Alphey et al., 2011b) and its business plan depends on repeated payments for ongoing releases (GeneWatch UK, 2010). This 50-year timescale now seems rather over-optimistic given the poor performance in the field (PAT, 2012; GeneWatch UK, 2012). It is therefore difficult to understand why the draft Guidance refers to "eradication" (although in theory eradication might be feasible with a different technology, such applications do not appear to be close to market). Lines 3724-3725: Fifty years is not really a "limited time" (see comments on line 3719 above) and, in any case, eradication is not envisaged over this time frame, merely continued population suppression (this in itself is questionable, given the many mechanisms for loss of fitness or development of resistance). There are also many mechanisms through which adult (flying) insects and particularly eggs might be transported to areas other than the release site. For example, the invasive species Aedes albopictus is thought to have spread worldwide via ships and tyres and agricultural pests spread via shipments of fruit, vegetables and other plant material etc. Because conditional lethality is partial and conditional, it is therefore deeply questionable whether GM insects will remain restricted limited area. For example, many mosquito species breed in septic tanks (Barrera et al., 2008) where sewage may be contaminated by tetracycline, allowing Oxitec's GM mosquitoes to survive and breed, perhaps for multiple generations (GeneWatch UK, 2012). Depending on the species, some insects eggs can remain dormant and survive dessication with larvae re-emerging at a later date (see e.g. Reiter et al., 1995: CDC, undated).
594	GeneWatch UK	GBR	4.2.4 Interactions of the GM insect with non-target organisms	Lines 3627-3629: There is a complete absence here of any discussion of the importance of restricting receiving environments (see for example comments on Lines 3565-3568). It is virtually inconceivable that a GM insect will be authorised for release across the whole of the EU because of the risk of establishing agricultural pest or disease vectors species where they do not currently exist. See also the discussion of strains above e.g. lines 867-877 i.e. introduction of non-native strains is also problematic and not compatible with plant pest regulations. The idea of introducing non-native beneficial insects such as bees is also deeply problematic. This means that risk management strategies MUST include measures to restrict transport and dispersal of eggs (deliberate or accidental), larvae and adults, and to limit the spread of the releases to the authorised receiving environment only. Whether this is any way practical or achievable is of course questionable, but this issue cannot be simply ignored. For example, controls are likely to be needed on fruit and vegetables containing GM eggs or larvae as 100% penetrance of lethality traits cannot be guaranteed. If an eradication approach were really achievable this might be less problematic as the marketing of fruit and vegetables could be suspended during the release programme, the crops could be destroyed, and it might be possible to allow resumption of marketing once sufficient monitoring had established the absence of the pest. But Oxitec's concept of ongoing releases to achieve population suppression implies that fruit and vegetables containing GM eggs and larvae would continue to be marketed throughout perhaps decades of releases (see also comments on Lines 3724-3725). See also comments on lines 185-186, regarding traceability and labelling. Lines 3636-3638: Not only the numbers but also population structure (e.g. age, size) can affect disease transmission so these need monitoring too. Line 3648: Applicants should also indicate how loss of efficacy would be detected and managed.

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595	GeneWatch UK	GBR	Step 5: Risk management strategies	Lines 3627-3629: There is a complete absence here of any discussion of the importance of restricting receiving environments (see for example comments on Lines 3565-3568). It is virtually inconceivable that a GM insect will be authorised for release across the whole of the EU because of the risk of establishing agricultural pest or disease vectors species where they do not currently exist. See also the discussion of strains above e.g. lines 867-877 i.e. introduction of non-native strains is also problematic and not compatible with plant pest regulations. The idea of introducing non-native beneficial insects such as bees is also deeply problematic. This means that risk management strategies MUST include measures to restrict transport and dispersal of eggs (deliberate or accidental), larvae and adults, and to limit the spread of the releases to the authorised receiving environment only. Whether this is any way practical or achievable is of course questionable, but this issue cannot be simply ignored. For example, controls are likely to be needed on fruit and vegetables containing GM eggs or larvae as 100% penetrance of lethality traits cannot be guaranteed. If an eradication approach were really achievable this might be less problematic as the marketing of fruit and vegetables could be suspended during the release programme, the crops could be destroyed, and it might be possible to allow resumption of marketing once sufficient monitoring had established the absence of the pest. But Oxitec's concept of ongoing releases to achieve population suppression implies that fruit and vegetables containing GM eggs and larvae would continue to be marketed throughout perhaps decades of releases (see also comments on Lines 3724-3725). See also comments on lines 185-186, regarding traceability and labelling. Lines 3636-3638: Not only the numbers but also population structure (e.g. age, size) can affect disease transmission so these need monitoring too. Line 3648: Applicants should also indicate how loss of efficacy would be detected and managed.
596	GeneWatch UK	GBR	Step 4: Risk characterisation	Lines 3586-3590: Lines 3591-3591: The use of the word "sterile" should be avoided: GM insects to date are not sterile but have a late-acting lethality trait that is partial and conditional. The possibility that GM insects with such traits become self-sustaining is only one aspect of impacts on target populations (and hence on ecosystems and endpoints such as human disease and crop damage). Even if the GM insects to do not become self-sustaining they are intended to have a significant effect on the target population (a population suppression effect) which can pose risks through a variety of mechanisms. There does not seem to be any consideration here of the dispersal of insect eggs and the timeframe for releases: it is unclear to the reader why these issues do not crop up until the section on non-target organisms, see comments on lines 3724-3725 Lines 3596-3597: It is not in principle correct to assume that ecosystems will revert to the original status after releases are stopped since they may exhibit hysteresis e.g. target populations could rebound after an initial suppression effect; other species may move into the ecological niche and become established; viruses could evolve, extinctions could occur etc. Some effects may not be reversible. Line 3598: Inherited lethality is partial and conditional in the case of Oxitec's RIDL insects. Lines 3601-3602: In some circumstances, loss of efficacy can increase adverse impacts beyond original levels e.g. via a rebound in populations or disease impacts. Lines 3603-3605: Oxitec's fluorescent marker fails in ovitraps in hot weather (Walters et al., 2012). Markers should be tested. Lines 3607-3610: Expected loss of fitness (e.g. through the "colony effect") and all mechanisms for development of resistance should also be considered. Lines 3614-3615: Resistance is expected to develop and loss of fitness will occur through the "colony effect": these are not unexpected effects. Lines 3616-3617: Preventative releases are problematic: see comments on lines 3565-3568. Lines 3620-3621: An ecosystem approach is needed: see comments on lines 3527-3529. Population suppression approaches can also lead to fluctuations in target populations and/or increases in populations in neighbouring areas (Yakob et al. 2008). Lines 3624-3625: These issues also apply to population suppression strategies

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597	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 3565-3568: It is questionable whether preventative releases would be compatible with plant pest control regulations since the concept of a "preventative" release implies that a GM pest would be released where the wild pest does not currently exist. This risks establishment of the pest in the release area: e.g. because conditional lethality is not fully penetrant, resistance develops, or the necessary conditions to ensure lethality are not met (e.g. in Oxitec's case, through exposure to tetracycline in the environment, which acts as a chemical switch for the lethality trait). The concept of preventative releases is even more questionable in the case of disease vectors such as Aedes albopictus, currently present in Italy (by far the most heavily infested country in Europe) and posing a potential health hazard to the rest of the EU (Hansford et al., 2010; ECDC, 2009). Is EFSA really suggesting that preventative releases of GM Aedes albopictus would be allowed in areas where this mosquito is not yet established? Why is there no discussion of the receiving environment in this section? Establishment of the baseline of the target species and of non-target species, as well as the presence of humans who may be bitten is critical. It is not clear how an EU-wide market approval can be applied to mass releases of GM insects given the major problem that target species will be established in some environments and not others (and at varying densities) and that the response to population suppression will depend on the ecosystem (e.g. density dependent effects). Thus, even if it were possible to establish that GM insect releases might have a beneficial effect in one area (e.g. reduction of a pest species or disease vector with a genuine sustained reduction in crop damage or disease incidence) the same GM insect releases might have a harmful effect elsewhere (e.g. establishment of a new pest species or disease vector in an area whether this species or strain had not been a problem). More complex effects might also occur in some areas but not others (e.g. competitive displacement by a more invasive pest species, effects on human immunity etc.).
598	GeneWatch UK	GBR	Step 3: Exposure characterisation	Line 3535: Stability is not only important for replacement strategies but also for population suppression strategies, as loss of efficacy can result in a rebound in the numbers of pests etc. In the case of disease vectors this can cause a rebound in cases of disease (Curtis et al., 2003; Scott & Morrison, 2003; Egger et al., 2008). A key difference between the Sterile Insect Technique (SIT) using irradiated insects and the release of genetically modified (GM) insects is that radiation-induced sterility involves multiple chromosome breaks, whereas the RIDL system relies on a specific genetic modification. Radiation-induced sterility therefore has built-in redundancy that is not provided by molecular genetic approaches. A number of authors have therefore speculated that any genetic or molecular event that allows the GM mosquitoes to survive and breed successfully could therefore be rapidly selected for during mass production (Benedict & Robinson, 2003; Robinson et al., 2004). If this happens, the conditional lethality effect could rapidly disappear as resistance develops in production facilities or in the field. Experimental data are therefore needed on resistance. Mechanisms other than selection for mutations during mass production may also be important such as female insects developing strategies to avoid mating with GM males or increased multiple mating (Hibino & Iwahashi, 1991; Helinski et al., 2012). Strains must be reported and re-tested if new GM strains are introduced periodically to counter the "colony effect" as new strains may have different properties (e.g. disease transmission or insecticide resistance). Lines 3550-3553: Markers should be tested. Lines 3556-3558: The type and extent of density-dependence in populations plays an important role in determining whether a population suppression approach will have a positive, neutral or negative effect (Juliano, 2007; Gould & Schliekelman, 2004; Walsh et al., 2011; Walsh et al., 2012; Barclay, 2001). Density-dependent effects at all life stages (e.g. larvae, pupae, adult) must therefore be reported for the receiving environment. Density dependence e.g. the effects of larval interactions on mosquito populations are different in different contexts, because they may be altered by ecological conditions (Juliano, 2009).
599	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 3527-3529: This section should also recognise the importance of interactions between effects on target and non-target organisms i.e. the importance of an ecosystem approach. For example, an initial reduction in the target organism using a population suppression approach could reduce the abundance of predators and increase the availability of food supplies, breeding sites or prey, but these initial effects could create further feedbacks on the target population, e.g. reduced predators and reduced competition for resources could lead to a rebound in the target population. Lines 3530-3532: Expected and actual release ratios and mating competitiveness should be reported: for example, the release ratio for Oxitec's experiments in the Cayman Islands has not been published and release ratios in experiments in Brazil have reached up to fifty-four GM mosquitoes to one wild mosquito (GeneWatch UK, 2012; PAT, 2012). The mating competitiveness was only 0.03 (3 in 100) on average and dropped to 0.012 (1.2 in 100) in the final phase in the Brazil experiments. This is an indication of poor efficacy in suppressing the wild mosquito population and could be used to make a comparison with similar parameters expected for the Sterile Insect Technique (SIT) as suggested in Lines 447-450. Tests should be conducted on conditional lethality and other traits to assess the penetrance of the trait under varying laboratory and environmental conditions (e.g. the dose-response curve to tetracycline is an important parameter which varies for different lines of Oxitec's GM insects, see e.g. Ant et al., 2012). Mechanisms through which laboratory conditions which allow breeding and survival in the lab may be encountered in the wild must be reported, e.g. tetracycline (which acts as a chemical switch for Oxitec's conditional lethality trait) is widely used in medicine and agriculture and can be found in

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				sewage, slurry and food products. An Oxitec laboratory protocol reports a 15% survival rate of its GM mosquitoes when fed cat food containing industrially farmed chicken, which contained sufficient levels of tetracycline (or an analogue of tetracycline) to overcome the lethality trait despite heat treatment (Nimmo et al., undated). It is also important to report the strain released (which may influence important properties such as disease transmission and insecticide resistance).
600	GeneWatch UK	GBR	Step 2: Hazard characterisation	Lines 3522-3525: Expected outcomes in release sites and neighbouring areas are both needed (because there is a possibility that populations increase in areas surrounding the release site): expected release ratios must be reported. Markers must be tested.
601	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 3502-3508: The introduction of new parent strains can also be problematic, due to altered disease transmission or insecticide resistance, see comments on lines 867-877. The 'colony effect' can have severe impacts on male mating fitness (IAEA, undated): this may affect gene drive mechanisms and the ability to replace wild-type populations with the GM trait.
602	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 3375: Markers must be tested for reliability: for example Oxitec's fluorescent marker began to disappear after 4 days in ovitraps at high temperatures (Walters et al., 2012). Lines 3379-3382: Stability should be assessed (not merely considered). Lines 3382-338: It is unclear how easily colonies can be renewed with local wild-types in the case of GM insects because the wild-type cannot be simply irradiated (as is the case with SIT) but a new transgenic line will have to be developed: any such lines must be fully tested to ensure they are consistent with the Environmental Risk Assessment (ERA) and account must be taken of pest control regulations and the potential differences in disease transmission and insecticide resistance between strains (see comments on lines 867-877). All potential means of developing resistance should be assessed (see comments on lines 3037-3039) and other mechanisms that may limit efficacy in either the short or long term, such as multiple mating (Helinski et al. 2012; Patil et al., 2012) and loss of mating fitness through the colony effect (IAEA, undated). Failure of conditional lethality or female lethality mechanisms can also occur in the presence of e.g. tetracycline contamination, in the case of Oxitec's technology, because tetracycline is used as a chemical switch which allows the breeding of insects in the lab. Data must be presented show penetrance of the conditional lethality or female killing trait in the presence of tetracycline; and levels in the environment (e.g. in sewage, industrially farmed meat etc.) must be established. Lines 3389-3396: Initial success of suppression followed by subsequent failure can lead to irreversible effects (such as establishment of an alternative invasive pests, see comments on Section 4.2.4; or reduction in human immunity, leading to a rebound in cases of disease, see comments on Section 4.2.6). There may be implications of introducing population suppression approaches for insect population management techniques more broadly, such as the need to prevent the use of some techniques which could interfere with the release programme, see comments on Section 4.2.5. These changes in management could affect the control of disease vectors and pests. Lines 3397-3399: A step-by-step approach must be taken to any experiments, so that open release experiments are not conducted prematurely, see paragraph (24) of Directive 2001/18/EC (EC, 2001). Lines 3402-3413: The introduction of new parent strains can be problematic, due to altered disease transmission or insecticide resistance, see comments on lines 867-877. The 'colony effect' can have severe impacts on male mating fitness, considerably reducing the efficacy of population suppression programmes (IAEA, undated). Line 3425: If mass releases of infected male mosquitoes occur this can be problematic even though male mosquitoes do not bite, because e.g. male Aedes Aegypti infected with the chikungunya virus can infect female Aedes Aegypti during mating, and may mate with multiple females (Mavale et al., 2010; Bargielowski et al., 2011). Releases are also likely to include some females due to imperfect sorting (Reeves et al., 2012). Lines 3429-3430: Strain and size may also be important for disease transmission and other properties. Lines 3448-3451: Properties such as pest-resistance and pesticide-resistance should also be mentioned.

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				Line 3455: Markers should be tested for reliability in a range of conditions. Lines 3487-3492: The introduction of new parent strains can be problematic, due to altered disease transmission or insecticide resistance, see comments on lines 867-877. Lines 3495-3499: Strain and size may also be important for disease transmission and other properties.
603	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 3369-3373: This section should be clear that a step-by-step approach to releases must be followed, so open release experiments are not conducted prematurely, see paragraph (24) of Directive 2001/19/EC (EC, 2001). Predictions should be made using computer models, calibrated with data from the lab and caged trials and validated at each stage before moving to open releases: multiple conceptual models must be considered to develop worst-case scenarios. Care must be taken to establish baselines of wild populations (which will fluctuate in different conditions, seasons etc.): since one of the predicted potential harms of SIT is a possible increase in target populations in surrounding areas (Atkinson et al., 2007; Yakob et al., 2011; White et al., 2010): a simple comparison of population levels in the target area with a neighbouring area is insufficient to establish a beneficial effect. Adverse effects which occur outside the release area also need to be identifiable and distinguishable from natural fluctuations. Population density as a result of GM insect releases may fluctuate with time, suffer an increase due to reduced effectiveness of the releases (e.g. due to developing resistance) and vary in and around the release site. Conditional lethality will result in large numbers of dead larvae, the numbers and distribution of these should be established in order to assess their potential impacts on biotic and abiotic processes. Female-killing or female-flightless approaches may also result in the survival of multiple generations of GM males and dead females: the numbers and distribution of these should be established. For disease prevention, the ultimate endpoint is disease incidence and severity (James et al., 2011): it is important that this is assessed because successful population suppression does not necessarily mean less, or less severe, disease , due to issues such as disease transmission thresholds and human immunity and cross-immunity (see comments on Section 4.2.6). Again, multiple conceptual models need to be considered to identify worst-case scenarios: for example, Oxitec's models of dengue transmission (Yakob et al., 2008; Alphey et al., 2011b) omit the important effects of cross-immunity on the incidence of dengue haemorrhagic fever and thus assume that only beneficial impacts on disease impacts can occur, when in practice there could be significant harm if population suppression in high-transmission areas is only partially effective (Thammapalo et al., 2008; Nagao & Koelle, 2008; GeneWatch UK, 2012). If the right concepts and mechanisms are not in the model in the first place, potentially serious risks may not be identified. For agricultural pests, crop damage will need to be assessed. Endpoints will also be needed for other potential applications such as enhanced pollinators.
604	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 3363-3365: The claim that population suppression of a non-native pest "should help to restore the environment to the state prior to the establishment of the non-native pest" is speculative: firstly, this depends on efficacy and whether the pest is really eradicated or e.g. only temporarily suppressed; secondly, there is hysteresis in environmental systems and non-linear effects meaning a return to some kind of former state is an over-simplification; thirdly, removing or reducing a pest (even if non-native) can cause increases in competitor pest species or reductions in beneficial species, or complex effects on human immunity i.e. adverse effects may also occur (see later comments). For native and non-native species the implications of reducing one component of a complex ecological effect may be difficult to predict. In the case of preventative release, there is a lack of current harm from the target pest and plans to introduce releases of a GM pest must consider the potential for survival and introduction of the pest (Section 4.2.1) due to incomplete penetrance or other mechanisms through which it might survive and breed. The issue of introduction of non-native strains as parent strains of the GM insect, as well as non-native species, should be fully considered in this section, along with the compatibility of such proposals with plant pest regulations, see comments on Lines 867-877.

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605	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 3342: The term “sterility” should be avoided, see comments on line 3061. Lethality may be female specific in some applications. Lines 3352-3356: are based on claims of efficacy, rather than demonstration of efficacy. For example, Oxitec has claimed it achieved an 80% reduction in the wild-type mosquito population during experiments in the Cayman Islands in 2010, but the company has not published these results so the release ratio and details of the experiment are not open to independent scientific scrutiny (GeneWatch UK, 2012). Results of Oxitec’s experiments in Brazil are poor, with a release ratio of fifty-four to one being required to achieve any noticeable effect in a small suburban area (PAT, 2012). Information on both short-term and long-term efficacy is critically important for population suppression programmes, especially for disease vectors (see comments on Section 4.2.6). Failure to publish results is not consistent with the step-by-step approach required by paragraph (24) of Directive 2001/19/EC (EC, 2001). The applicant should be required to: (1) Provide evidence on mating fitness and on the expected release ratio of GM to wild-type insects required for a given population suppression effect in a given receiving environment; (2) Consider unintended effects on population dynamics such as fluctuations in target insect populations; influx of insects from surrounding areas; potential increases in target insects in surrounding or target areas: some models exist (e.g. Atkinson et al., 2007; Yakob et al., 2011; White et al., 2010) but have not been validated; (3) Consider any changes to population structure, especially where these may have impacts considered in other subsections e.g. transmission of some diseases may be related to mosquito size (Alto et al., 2008); (4) Consider the mechanism and impacts of developing resistance (see comments on lines 3037-3039) and other mechanisms that may limit efficacy in either the short or long term, such as multiple mating (Helinski et al. 2012; Patil et al., 2012) and loss of mating fitness through the colony effect (IAEA, undated); (5) Quantify numbers of dead and surviving GM insects in a variety of scenarios, including numbers of dead larvae or pupae using a late-acting lethality trait, numbers of surviving males and dead adult females in each generation using female-specific approaches; numbers of surviving progeny, including females, taking account of limitations in penetrance conditionality etc. (e.g. exposure to tetracycline where this is used as a chemical switch for conditional lethality). Lines 3356-3357: Should not refer to “sterile” insects: there are no sterile GM insects currently being considered for release, see comments on Lines 2983-2984, 3061 etc. etc.
606	GeneWatch UK	GBR	4.2.3 Interactions of the GM insects with target organisms	Line 3318: The use of the phrase “commonly applied” in relation to SIT programmes is misleading. SIT has been used successfully with some agricultural pest species, but has been less successful with others because different insect species have very life histories and behaviours. In general SIT is not effective at reducing large populations of insects without other interventions, but may be effective at reducing or eradicating smaller, isolated populations (Klassen, 2005). SIT has not generally been successful for mosquitoes, where population suppression has been achieved only in a few experiments with very large “release ratios” of sterile to wild mosquitoes (Spielman, 2003; Asman et al., 1981; McDonald et al., 1977). Lines 3324-3325: The use of the term sterile should be avoided as it implies the insects do not reproduce: a conditional-lethality trait allows the insects to reproduce in the lab and also in the wild, although the intention is that the majority of the progeny die at the larval stage. See comments on lines 3047-3051. Large-scale releases of GM insects with conditional lethality or female-specific traits (e.g. female killing, flightless-female) are intended to have significant impacts on the target organism by suppressing or eliminating the population. Changes in the size, distribution and age structure of the target population will then have knock on effects on other organisms via interactions with predators, prey, competitors etc. (see Section 4.2.4) and potentially on pathogens, infections and diseases (missing section) and human and animal health (Section 4.2.6). Effects on non-target organisms may in turn alter the population dynamics of the target organism. For population suppression approaches the efficacy of the approach will need to be considered (i.e. whether the target population is suppressed and whether this is sustained), including the release ratios to achieve a given effect on population and any unintended or unwanted effects on the target population e.g. fluctuations in target population, increases in the target population outside the release area, influx of wild-type insects from surrounding areas. Indirect effects will include interactions with non-target species e.g. if a predator population falls as a result of an initial population suppression effect, the target population might rebound. Line 3326: Add: pest-resistance and pesticide-resistance. Lines 3333-3334: Adverse effects may not be reversible even if the GM insect population dies out, due to changes in population dynamics (including the elimination of a species, or alterations in numbers of predators, competitors or prey).
607	GeneWatch UK	GBR	Step 5: Risk management strategies	Lines: 3090-3092: Specific conditions may be required in terms of receiving environments or geographical areas, as noted in paragraph 1, Article 19, Directive 2001/19/EC. In particular, possible establishment of a species or strain of a pest or disease vector in an area where that species or strain of pest or disease vector is not present must be avoided.

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608	GeneWatch UK	GBR	Step 4: Risk characterisation	Lines 3073-3076: Where uncertainties exist multiple conceptual models must be considered (e.g. Alphey et al., 2011a) and requirements for model validation followed.
609	GeneWatch UK	GBR	Step 3: Exposure characterisation	Line 3061: The use of the term sterile should be avoided as it implies the insects do not reproduce: a conditional-lethality trait allows the insects to reproduce in the lab and also in the wild, although the intention is that the majority of the progeny die at the larval stage; female-killing or flightless-female approaches are also intended to have population suppression effects but are not sterile. “Sterility” implies no vertical gene transfer, which is not the case. See comments on lines 3047-3051.
610	GeneWatch UK	GBR	Step 2: Hazard characterisation	Line 3066-3069: Escape is also relevant at the production and transport stages for GM insects which are intended to be released into the wild, as problems may occur in particular receiving environments e.g. if GM Aedes albopictus intended for release in a population suppression programme in Italy escape in France this could lead to the establishment of this invasive species. Information on conditionality, penetrance, stability, potential to develop resistance etc. is required as described above (see comments on Lines 3037-3039).
611	GeneWatch UK	GBR	Step 2: Hazard characterisation	Lines 3037-3039: Restriction of this section to considering only “enhanced fitness” is wrong. Penetrance and survival of GM insects with reduced fitness traits such as conditional lethality or female-killing traits must also be considered in a range of conditions (including the conditions used to breed the insects in the lab e.g. presence of tetracycline). See comments on line 2957 above: the Directive (EC, 2001) refers explicitly to advantage or disadvantage. This section should also consider the risks associated with the introduction of non-native parent species and strains, which may have altered capacity to transmit diseases or insecticide-resistance, see comments on lines 867-877. Applicants should be required to specify the parent strain and test its properties: any proposed releases will also need to be compatible with plant pest regulations. Data must also be supplied on the stability and persistence of the trait and the development of resistance should to be considered. For example, radiation-induced sterility (which involves multiple chromosome breaks) has built-in redundancy that is not provided by molecular genetic approaches: this raises the possibility that any genetic or molecular event that allows the GM mosquitoes to survive and breed successfully could therefore be rapidly selected for during mass production (Benedict & Robinson, 2003; Robinson et al., 2004; Alphey et al., 2011a). If this happens, a conditional lethality effect could rapidly disappear as resistance develops in production facilities or in the field and vertical gene transmission in the field would increase significantly. Other mechanisms of resistance include wild females appearing that are unreceptive to mating with the transgenic males, as occurred in one study with SIT (Hibino & Iwahashi, 1991). Loss of gene expression in a virus resistant GM mosquito has also been reported (Franz et al., 1991). Stability of the trait must also be demonstrated (Adelman et al., 2004). Lines 3047-3051: The use of the word sterility is misleading. Oxitec’s GM insects have a conditional lethality trait (Phuc et al., 2007) and/or a conditional female-killing or female-sorting (Morrison et al., 2010) or female-flightless trait (Labbé et al., 2012), usually combined with a heritable fluorescent marker. Vertical gene transfer therefore occurs to the next generation, via mating in the wild. This requires data to be provided on (1) conditionality (i.e. the extent to which the conditions used for breeding in the lab may occur in the wild); (2) life stage of late-lethality or other non-sterile traits (for example, percentage that die as larvae or pupae etc.); (2) penetrance under different conditions (i.e. the numbers that express the trait and die prematurely or are flightless etc.). If genetic markers are used to establish frequency of survival, the reliability of the market itself must be established (Walters et al., 2012). In the case of female-only traits (flightless females or female-killing) the dispersal of males must be considered. Lines 3052-3054: Vertical gene transfer within the greenhouse to the target species (with which the GM insect will mate) also needs to be described. Escape may occur during production, transport and use and may occur through a variety of mechanisms at all life stages (e.g. flying, transport of eggs or larvae on workers or materials carried in or out, including the crop).

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612	GeneWatch UK	GBR	4.2.1 Persistence and invasiveness, including vertical gene transfer	Lines 2995-2998: This section should mention disease-resistance and pesticide-resistance as traits that could enhance fitness (see comments on Lines 2954-2955). Traits that could reduce fitness (e.g. a conditional lethality trait) will also be passed to the same species through mating (vertical gene transfer): applicants should provide information on: (1) penetrance of the loss-of-fitness trait in a variety of experimental conditions; (2) tests on conditionality i.e. on whether insects bred in the lab could also breed in the wild in the presence of contaminants e.g. Oxitec's RIDL technology relies on the common antibiotic tetracycline as a chemical switch to allow breeding in the lab, but feeding the mosquitoes on cat food presumed to be contaminated with tetracycline allowed a 15% survival rate, compared to 3-4% survival rate on a normal diet (Nimmo et al., undated). It should be clear to applicants that this kind of information should not be withheld as commercially confidential (House of Lords Hansard, 2011). Experimental data should be provided regarding the penetrance of the trait in the presence of different levels of tetracycline and its analogues. Lines 2999-3003: Other traits could also presumably cause negative impacts as a result of cross-mating. Line 3004: the use of the word sterile should be avoided, see comments on Lines 2983-2984. Other issues on which data needs to be provided are: (1) stage of the life-cycle at which any conditional lethality trait acts, because e.g. late acting lethality in pests may lead to substantial damage to crops at the caterpillar stage (see e.g. page 26 of Umweltbundesamt, 2010); (2) for female-killing approaches (including flightless females), possible harms may be caused by surviving males e.g. whilst male mosquitoes do not bite, male Aedes Aegypti infected with the chikungunya virus can infect female Aedes Aegypti during mating, and may mate with multiple females (Mavale et al., 2010; Bargielowski et al., 2011); male flies may transfer pathogens from faeces to food Lines 3011-3016: Insects with limited reproductive capacity, developed for use in population suppression approaches, can also have significant effects on ecosystems (these issues should be discussed further in Sections 4.2.3 and 4.2.4.). Mating fitness is also an important parameter in such programmes (to be discussed further in Section 4.2.3). Line 3018: Should mention pest-resistance and pesticide-resistance as well as drought tolerance. Line 3027-3030; It is unclear why intentional releases into environments other than those already inhabited by the species of interest are being contemplated: even non-native strains (let alone non-native species) need strict control. Attempts by Oxitec to release a genetically-engineered North American strain of diamond back moth in the UK have already caused problems due to plant pest regulations (HSE, 2011a&b; DEFRA, 2012; FERA, 2012).
613	GeneWatch UK	GBR	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 2983-2984: GM insects currently being considered for release in population suppression approaches are not sterile: the term sterile should be avoided. Oxitec's GM mosquitoes have a conditional lethality trait: this is conditional because it relies on tetracycline as a chemical switch to allow breeding in the lab; partial because it does not have full penetrance; and late-acting i.e. the insects are not sterile but mate and reproduce with most dying at the late larval stage (in the absence of tetracycline) (Phuc et al., 2007). The use of the term sterile is misleading because it implies there is no exposure to female biting GM mosquitoes or prospect of survival and breeding of the GM mosquitoes in the environment, which is incorrect. This section also requires a description of female-killing approaches, such as female-specific flightless Aedes albopictus (Labbé et al., 2012) and female-specific lethality in Diamond back moth (Plutella xylostella) (Annex 1 to HSE, 2011a; Oxitec, 2011b; Martins et al., 2012) and tomato borer (Tuta absoluta) (Morrison et al., 2011) as these approaches to population suppression are also significantly different from "sterility". Note that the flightless-female mosquito application does not directly kill the insects, but the females die due to inability to seek out blood to feed. Oxitec's GM Aedes albopictus could in theory be used in the EU; Oxitec has already attempted to obtain permission release GM diamond back moths in the UK (arguing that release in open field or polytunnels could be treated as a "contained use" application due to claimed "biological containment") and has cited 2013 as its target date for trials of GM tomato borers: such trials could take place in the EU. Line 2994: This section should also consider the risks associated with the introduction of non-native parent species and strains, which may have altered capacity to transmit diseases or insecticide-resistance, see comments on lines 867-877. Applicants should be required to specify the parent strain and test its properties: any proposed releases will also need to be compatible with plant pest regulations.

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614	GeneWatch UK	GBR	4.2.1 Persistence and invasiveness, including vertical gene transfer	Line 2957: The title and content of this section could be taken to imply that only GM insects that are more invasive or persistent that their wild counterparts can have adverse effects on the environment or human or animal health. This is because the specific issue in D.1 of Annex II of the Directive (Likelihood of the GMO to become persistent and invasive) is being conflated with the whole issue of vertical gene transfer. The first three issues listed in Annex II D.1 of Directive 2001/18/EC are: 1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s); 2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s); 3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species [emphasis added]. The population suppression approach relies on releasing insects that are less able to reproduce than their wild counterparts (via a conditional lethality or female-killing approach), which are intended to mate with the wild insects and significantly reduce the wild population: many of the environmental and human health issue with this approach associated with vertical gene transfer are not associated with persistence and invasiveness, but relate to the impacts of the releases on the target species (covered in Section 4.2.3) and non-target species. However, the disadvantage conferred to the GMO (or other species if cross-mating occurs) need to be considered here, including whether it will be realised under the release conditions. Issues that need to be discussed in this subsection include: (1) circumstances under which the conditional lethality approach may fail, leading to breeding and survival of future generations of GM insects; (2) adverse effects of expected male insect survivors under a female-killing approach: (3) adverse effects of unintended female GM insect survivors. However, it should also be noted that releases of GM insects in a population suppression approach are intended to disrupt the population dynamics of the target species (discussed further in Section 4.2.3) and that this will have further knock-on effects on non-target species (discussed further in Section 4.2.4) and pathogens (missing section). It is important that the definition of “target organism” is clear throughout the guidance so that readers are aware that impacts of the GMO on the wild-type organism are considered in Section 4.3.2.
615	GeneWatch UK	GBR	4.2 Specific areas of risk for the ERA of GM insects	Lines 2954-2955: This description is inadequate to give the reader any insight into proposed applications. The concept of GM bees engineered to be more efficient pollinators is mentioned several times throughout the text but no references are given. Other potential applications, such as pest-resistant or pesticide-resistant bees (or other beneficial insects, such as butterflies: Marcus et al., 2004) are not mentioned at all. Research on the honey bee (Apis mellifera) has included some laboratory research on insecticide-resistance (cited in Beech et al., 2012) and genetic modification may one tool considered by researchers who wish to create bees that are more resistant to pests or diseases (Zakaib, 2011). Insecticide-resistant beneficial insects, including bees, might lead to increased use of insecticides. Transgenic silkworms with a high antiviral capacity have recently been created (Jiang et al., 2012): this raises a whole set of new questions about interactions between viruses and silkworms: for example, would viruses evolve to become more virulent? Could similar traits be applied to other insects (e.g. bees)?
616	GeneWatch UK	GBR	4.2 Specific areas of risk for the ERA of GM insects	Lines 2949-2950: It is misleading to state that chemical insecticides are the current primary means of controlling insects causing public health concerns, although they can certainly play an important role. For example, in the case of Aedes aegypti (a vector for dengue), destruction of breeding sites by government programmes and/or community programmes is one of the main interventions, although this is often accompanied by the routine use of larvicides and by the use of adulticides during epidemics, as well as mosquito traps (Florida Mosquito Control, 2009; Baly et al., 2009; Egger et al., 2008). Provision of piped water, because water storage containers used by households without tap water supply provide mosquito breeding sites, is also an important intervention (Schmidt et al., 2001). Some biological control programmes have been successful in Vietnam (Nam et al., 2005; Kay & Nam, 2005). It is also unclear the extent to which species-specific population suppression approaches could replace insecticide use (even if population suppression approaches using GM insects are effective, which is questionable) because there are often multiple species involved in disease transmission or simply present as a nuisance species which need to be controlled. For example, in Cayman, where Oxitec has conducted open release experiments using GM Aedes aegypti mosquitoes, aerial spraying is mainly not related to this dengue-transmitting species but to the swamp species Aedes taeniorhynchus (Anon, 2012a). The possibility of competitive displacement of one disease transmitting mosquito for another has been highlighted in risk assessment workshops for GM mosquitoes (Beech et al., 2009), although largely ignored in practice (GeneWatch UK, 2012): the issue of multiple species will also be important for malaria in many regions (Kiszewski et al., 2004) and will limit the role of species-specific GM approaches in reducing insecticide use even if the GM approach is effective at reducing disease transmission by the target species (which currently remains highly questionable).
617	GeneWatch UK	GBR	4.2 Specific areas of risk for the ERA of GM insects	2937: As noted above whole subsections are missing from this section, including: Pathogens, infections and diseases; Abiotic interactions; Impacts on animal health. In general, it is very unclear which issues should be addressed in which subsections, due to poor correspondence with the requirements of the Directive and inconsistencies throughout the Guidance (see comments on Lines 1825-1826). There is frequent mention of tropical diseases: it should be clear at the start whether the Guidance is intended to apply to EU applications only or also to the risk assessments required for transboundary notifications for exports of GMOs from the EU to overseas (see comments on Line 250). Oxitec has already made three transboundary notifications, for experimental releases of GM Aedes aegypti mosquitoes in Cayman, Malaysia and Brazil. The notifications and associated risk assessments were not made publicly available in advance of the trials (except in Malaysia where a summary risk assessment was published) and the risk assessments provide inadequate information (GeneWatch UK, 2012; Reeves et al., 2012). This issue of whether the

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				Guidance covers transboundary movements or not should have been clarified prior to consultation, otherwise it is hard to give meaningful responses, since different insect species and applications are likely overseas from those expected in the EU.
618	GeneWatch UK	GBR	Step 5: Risk management strategies	Line 2928: Reducing exposure to the GM fish itself will not help in situations where the pathogen is transmitted by another organism (e.g. non-GM fish which have been infected by the GM fish).
619	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 2897-2901: It is not only exposure to the GM fish itself that must be considered. Escapes or releases of the GM fish could alter ecosystems in a way that is harmful to human health through indirect pathways e.g. an increase in a harmful competitor species.
620	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2800: Reference Veenstra et al., 1992 is missing from the reference list.
621	GeneWatch UK	GBR	4.1.7 Impact on human health	Lines 2776-2778: It should be clarified whether GM fish not intended to be marketed as food or feed but which might nevertheless be inadvertently eaten will require a food safety evaluation e.g. GM daughterless carp released with the aim of reducing the wild carp population might be eaten even though the application is not for food/feed. A section on impacts on animal health is also needed: this should include impacts e.g. on pets or other wild species that might eat the fish (which are not necessarily included in the food safety assessment) or which might be exposed to it or incur risks via the environment (for example, pathogens transferred from the GM fish to other fish and then to another animal). Line 2780: Pathogens and parasites might also enter the food chain in increased levels in other species due to complex ecosystem interactions caused by the release of the GM fish.
622	GeneWatch UK	GBR	4.1.6 Environmental impacts of the specific techniques used for the management of GM fish	Line 2711: Data should be provided on changes in diet or feed consumption. For example, Aquabounty has conducted experiments during which transgenic salmon had rates of consumption that were approximately five times that of the control fish (Abrahams & Sutterlin, 1999).
623	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 2525: Potential increased exposure to pathogens due to indirect effects, such as increase of an infected competitor species due to the effects of the GM fish on wild wish, should be included.
624	GeneWatch UK	GBR	Step 2: Hazard characterisation	Lines 2491-2496; Add: d) any altered ecosystem effects expected as a result of the GM fish release or escape (see Section 4.1.3) that might change the spread of pathogens, even if they are not spread by the GM fish itself (e.g. this could be by a competitor species whose population has increased due to the impact of the GM fish releases on the target species). Lines 2497-2500: Information on infectivity of pathogens to competitor species is also required because harm could be caused by an increase in a competitor species.
625	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line: 2481: Add: Can the GM alter the spread of pathogens via its interactions with other components of the ecosystem e.g. an increase in competitor species that carry pathogens as the result of a population suppression effect?
626	GeneWatch UK	GBR	4.1.4 Pathogens, infections and diseases	Lines 2380-2383; A new section on animal health is also needed, which should include impacts of pathogens on animal health (i.e. not just humans). This should also consider contact with and consumption of other fish or aquatic organisms that may carry the pathogen as a result of the release or escape of the GM fish (see lines 2428-2431).

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627	GeneWatch UK	GBR	Step 6: Overall risk evaluation and conclusions	Line 2353-2354: It is not just long-term exposure but long-term impacts (e.g. potentially irreversible impacts as discussed in lines 2339-2342) that need to be considered.
628	GeneWatch UK	GBR	Step 5: Risk management strategies	Line 2344: Should say biota and ecosystems and key ecological functions. For example an increase in an invasive competitor species is not an adverse impact on that species or on an ecological function but may nevertheless be regarded as an adverse impact on the ecosystem.
629	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 2315-2316: correctly identify that it is the fish and its influences that must be considered. However, there is still a tendency to characterise exposure in a narrow sense which may exclude some of the hazards. For example, a GM fish that escapes and decimates the wild population due to a Trojan gene effect may have limited survival in the environment, but so will the wild species! In this scenario, even when all the GM fish are dead there may still be irreversible adverse effects on the ecosystem (including e.g. the loss of an endangered species). The same is true of population suppression approaches: whilst intended to remove an unwanted species (such as invasive carp) by mating with them, there could be unintended consequences on other species which might be irreversible (e.g. a loss of a predator species, or establishment of a competitor invasive species). These problems stem from the concept of “exposure characterisation” which has been borrowed from toxicology and is too narrow to encompass all the effects required to be considered in the ERA by Directive 2001/09/EC (EC, 2001). See comments on lines 386-391.
630	GeneWatch UK	GBR	Step 2: Hazard characterisation	Lines 2491-2496; Add: d) any altered ecosystem effects expected as a result of the GM fish release or escape (see Section 4.1.3) that might change the spread of pathogens, even if they are not spread by the GM fish itself (e.g. this could be by a competitor species whose population has increased due to the impact of the GM fish releases on the target species). Lines 2497-2500: Information on infectivity of pathogens to competitor species is also required because harm could be caused by an increase in a competitor species.
631	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line: 2481: Add: Can the GM alter the spread of pathogens via its interactions with other components of the ecosystem e.g. an increase in competitor species that carry pathogens as the result of a population suppression effect?
632	GeneWatch UK	GBR	4.1.4 Pathogens, infections and diseases	Lines 2380-2383; A new section on animal health is also needed, which should include impacts of pathogens on animal health (i.e. not just humans). This should also consider contact with and consumption of other fish or aquatic organisms that may carry the pathogen as a result of the release or escape of the GM fish (see lines 2428-2431).
633	GeneWatch UK	GBR	Step 6: Overall risk evaluation and conclusions	Line 2353-2354: It is not just long-term exposure but long-term impacts (e.g. potentially irreversible impacts as discussed in lines 2339-2342) that need to be considered.
634	GeneWatch UK	GBR	Step 5: Risk management strategies	Line 2344: Should say biota and ecosystems and key ecological functions. For example an increase in an invasive competitor species is not an adverse impact on that species or on an ecological function but may nevertheless be regarded as an adverse impact on the ecosystem.
635	GeneWatch UK	GBR	Step 3: Exposure characterisation	Lines 2315-2316: correctly identify that it is the fish and its influences that must be considered. However, there is still a tendency to characterise exposure in a narrow sense which may exclude some of the hazards. For example, a GM fish that escapes and decimates the wild population due to a Trojan gene effect may have limited survival in the environment, but so will the wild species! In this scenario, even when all the GM fish are dead there may still be irreversible adverse effects on the ecosystem (including e.g. the loss of an endangered species). The same is true of population suppression approaches: whilst intended to remove an unwanted species (such as invasive carp) by mating with them, there could be unintended consequences on other species which might be irreversible (e.g. a loss of a predator species, or establishment of a competitor invasive species). These problems stem from the concept of “exposure characterisation” which has been borrowed from toxicology and is too narrow to encompass all the effects required to be considered in the ERA by Directive 2001/09/EC (EC, 2001). See comments on lines 386-391.

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636	GeneWatch UK	GBR	Step 2: Hazard characterisation	Line 2263: Decreased competition (for example, if releases of the GMO reduce the numbers of the target species) can also be a problem if it allows numbers of an invasive or harmful species (e.g. a disease vector) to increase due to reduced competition for food, breeding sites etc. Lines 2275-227: Mating of the GM fish with wild fish can also reduce numbers if the offspring have reduced fitness or reproductive capacity (e.g. are all male): indeed this is one intended application for GM fish (a population suppression approach), as described above. Line 229: Should say changes in fish characteristics or fish populations and associated ecosystems. For example , if GM daughterless fish were released in order to try to remove an invasive species through mating and producing an all-male population which cannot breed, each individual fish may have the same relationship with symbiots as its wild counterpart, but the effects of the release programme as a whole could still have a significant effect on symbiots. The same problem might occur if an accidental release occurred of a GM fish which gave rise to the Trojan effect, or similar adverse effects, on wild populations. As is clear in Directive 2001/19/EC it is the characteristics of the GMO and the conditions of its release and its interactions with the receiving environment that are important. Lines 2294-2296: Models must be validated and the effects of alternative conceptual models must be explored. See comments on modelling above. Lines 2297-2303: Impacts on animal health merit an entire subsection, as has been included in the mammals and birds section. A single paragraph, whilst important to draw attention to the issue, is insufficient to address the requirements of the Directive, which includes this issue in step 7 of part D.1, Annex II (EC, 2001). Further, it is incorrect to imply that such assessments are less important for fish that are destined for human or animal consumption. This new subsection must include the impacts of the pathogens and diseases identified in Section 4.1.4 on other animals: with a focus on their possible transfer to other fish and/or transfer to or consumption by other animals. It should be noted that an assessment of food/feed safety of the GM fish under EFSA's other guidance does necessarily not apply to (1) other species eating the GM fish (i.e. not the species intended to be fed with it); or (2) any species eating other fish that have been infected with pathogens from GM fish.
637	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 2229-2256: It is unclear to the reader why the detail provided in the mammals and birds section (e.g. Figures 7, 8 and 9 and accompanying text) is not provided here.
638	GeneWatch UK	GBR	4.1.3 Impacts on biotic components and processes	Lines 2220-2222: Including all biotic effects (target and non-target) in one section, with a separate section for pathogens and diseases, makes it easier to follow an ecosystem approach (CBD, undated), which acknowledges complex interactions (for example, a reduction in the numbers of the target organism could reduce non-target predators and then increase the numbers of the target organism again). However, this approach differs from that used in the insects and mammals and birds sections: a consistent approach should be used throughout the guidance. The definition of target organism should also be consistent (see comments on lines 1832-1843): in the insects section it is taken to mean the organism that is genetically modified: it would be clearer if this definition is used throughout. For example, in the case of AquaBounty's GM salmon, what is the target organism (presumably it is Atlantic Salmon, Salmo salar?). This should be clear to the reader throughout.
639	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Line 2128: Bensasson et al., 2004 is missing from the reference list.
640	GeneWatch UK	GBR	Step 6: Overall risk evaluation and conclusions	Line 2067: Should include the extent to which the GM fish and offspring of matings are more or less successful.
641	GeneWatch UK	GBR	Step 5: Risk management strategies	Line 2059: Lowered sexual fertility of the GM fish may have negative impacts on wild populations if mating success is high but reproductive fitness low.

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642	GeneWatch UK	GBR	Step 4: Risk characterisation	Lines 2025-2026: Reduced reproductive fitness may mean negative impacts on wild population through mating and the production of less fit wild populations. Lines 2034-2043: If population changes are to be included here, the above comments on population suppression approaches must be taken into account. It would also be helpful, as noted above, if the sections on insects and mammals and birds were consistent so the reader knew which subsection these effects would appear in.
643	GeneWatch UK	GBR	Step 3: Exposure characterisation	Line 1998; Mitigation measures to reduce gene transfer such as reduced fertility can exacerbate other effects e.g. a population suppression effect on wild species (see comments on lines 1864-1936). There is a problem with the whole concept of "exposure characterisation" as it deals only with direct effects (analogous to toxicological effects) not with complex ecosystem interactions (see comments on lines 386-391).
644	GeneWatch UK	GBR	Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 1899-1900: Information on the parent fish strain must be provided. Lines 1864-1936: This entire section neglects consideration of potential applications of deliberate releases of GM fish, engineered to be partially sterile or create only male offspring which are intended to mate with and crash an invasive (unwanted) population of fish e.g. carp. This analogous to the population suppression approach discussed for GM insects and the theoretical example of the GM "sterile" rabbit, yet no equivalent example has been included for fish (except as an accidental outcome of escapes, i.e. the Trojan gene effect, lines 1947-1959). There are proposals for this type of application (i.e. the use if this and similar effects in a deliberate programme to remove unwanted species) and relevant technology has been patented (e.g. Nowak, 2002; Thresher, 2008; Aquabounty, 2011). The Guidance should be clear about whether this type of application is prohibited by existing legislation and conventions or whether it might be subject to an environmental risk assessment. If the latter, the flow chart needs to be much more sophisticated: the question "Will GM fish reproduce?" might lead to an answer: yes, but produce only (or, mostly) male offspring; or no, most or all offspring will not survive. In the latter case this means there is a reduced chance of the GM fish itself becoming invasive but this does not mean the ERA should be limited by the survival period of the GMO in receiving environments, as indicated in the flow chart (this is an error due to the mistaken focus on exposures, see comments on lines 386-391). In other words, the flowchart must recognise that production of infertile offspring (or reduced fitness, or single-sex offspring) can also lead to adverse effects. The main environmental impact of a population suppression programme using GM fish will be a significant reduction in the target species (or fluctuations in numbers, influx from surrounding areas, or other potential adverse effects if unsuccessful) and effects on non-target species could be significant (e.g. increase in competitors, reductions in prey, complex interactions etc.): these issues will need to be assessed, as this is a requirement of the Directive (EC, 2001). It is confusing for the reader to understand which subsection these impacts should be included in, due to the inconsistencies of the different sections on fish, insects and mammals and birds (see comments on lines 1825-1826). In the insects section, vertical gene transfer has been considered only in the context of persistence and invasiveness, and effects on population suppression have been considered (albeit poorly) in the section of effects on the target organism. This way of organising the information works but only if it is consistent between the different sections (fish, insects and mammals and birds) and the population suppression approach is considered in all sections. Further, it requires a consistent definition of "target organism" so that the reader is not confused (see comments on lines 1832-1843).
645	GeneWatch UK	GBR	4. Specific areas of risk to be addressed in the ERA	Lines 1825-1826: The inconsistencies between the three different sections are deeply problematic, particularly in the insects section where many important issues required in the ERA by Directive 2001/18/EC are not properly addressed. This section should firstly lay out in full the information on which conclusions need to be drawn as listed in Annex II D.1 of the Directive (EC, 2001). This would make clear, for example, that "Interactions with non-target organisms" means "Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens". All sections (Fish, insects, mammals and birds) should have subsections which match the requirements in D.1. It makes sense, however, to subdivide some of these, for example to include a subsection on "Pathogens, infections and diseases": the omission of this from the insects section is inexcusable since many insects are disease vectors. Subsections on impact on biogeochemical processes and impact on animal health also need to be included in the insects section: these are major areas of potential impact and there is no excuse for omitting them. A subsection on animal health is also needed in the fish section. These are significant gaps and it is likely that further consultation will be needed once they have been filled. Lines 1832-1843: The definition of target organism in the glossary creates considerable confusion between the sections: is it the organism that is genetically modified (as used in the insects section) or the parasites, pathogens or other species which are displaced or consumed by the animal (mammals and birds section)? In the latter case there may be multiple "target organisms" leading to further confusion: further, a population suppression approach might be used for mammals (the theoretical "sterile" rabbit example) in which case the target is presumably the animal itself. Again, the concept seems to have been borrowed from the risk assessment process for plants without proper thought. It would greatly help the clarity of the document if target organisms were defined as animals of the same species that is genetically modified, throughout. Alternatively, at least a

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				consistent definition must be used between all the sections.
646	GeneWatch UK	GBR	3.8.3 Health and welfare aspects for GM insects	Line 1821: There are a wide variety of other beneficial insects e.g. butterflies, ladybirds, not just bees.
647	GeneWatch UK	GBR	3.8.2 Health and welfare aspects for GM fish	Line 1817: Loss of genetic diversity needs to be considered as mass production of identical GM fish may increase vulnerability to infection.
648	GeneWatch UK	GBR	3.8.1 Health and welfare aspects for GM mammals and birds	Line 1797: Loss of genetic diversity needs to be considered as mass production of identical GM mammals or birds may increase vulnerability to infection.
649	GeneWatch UK	GBR	3.8 Aspects of GM animal health and welfare	Line 1752: The first production stage for GM animals involves establishing the transgenic trait. The process of obtaining eggs is invasive if taken from live mammals, and implanted genetically modified eggs lead to many stillbirths, miscarriages or invasive surgery on the mother (GeneWatch UK, 2002). Ethical issues are similar to those associated with cloning mammals (EGE, 2008) but have been entirely neglected here. Loss of genetic diversity (due to the production of genetically identical herds of cows or farmed chickens or fish) also needs to be considered as it may increase vulnerability of the animals to infection.
650	GeneWatch UK	GBR	3.7.3 Interplay between ERA conclusions and PMEM	Line 1727: Reversibility of effects and their potential seriousness should be considered (e.g. possible establishment of a more invasive disease vector, evolution of a virus, or adverse human health impacts due to effects on immunity). Line 1737: Monitoring methods should be tested for robustness e.g. Oxitec's transgenic fluorescent marker in bollworms begins to fail in ovitraps after as little as four days in hot weather (Walters et al., 2012).
651	GeneWatch UK	GBR	3.7.1 Introduction	Line 1579: Applicants and regulators should recognise that environmental models are generally mathematically ill-posed or ill-conditioned, meaning that the information content available to define a modelling problem does not allow a single mathematical solution (Baveye, 2003, Beven, 2002, 2003 and 2006). Even well-calibrated models (i.e. models fitted to the data at a particular site) can have no predictive value if the equations and structure of the model do not adequately represent processes that occur in the real world: this is true even for physical systems (e.g. Carter et al., 2006) but uncertainties and unknowns will be greater for biological systems. It is therefore critical to explore alternative conceptual models and assumptions which may lead to very different conclusions about risk (e.g. Medlock et al., 2009). Scientific bias can be classified into five types: confirmation bias, rescue bias, mechanism bias, "time will tell" bias and orientation bias (Kaptchuk, 2003) and the existence of bias in technology assessment has been well-documented, especially in the medical literature (e.g. Bhandari et al., 2004). It is therefore important to be transparent about subjective judgments contained in model assumptions or data analysis methodology and to explore a variety of alternative conceptual models and scenarios. For example, outputs of population models of a wide variety of species change significantly if the effects of environmental fluctuations are included. Failure to anticipate unexpected events can be exacerbated by the use of complex models which are only comprehended within a small expert group, because they are then less likely to be open to scrutiny or challenge by outsiders (Beken et al., 2010). Failure to act on early warnings and anticipate unexpected events (resulting in e.g. collapses in fish stocks, the effects of CFCs on the ozone later, and the harm to health caused by X-rays and asbestos) underpins the adoption of the precautionary principle in Directive 2001/18/EC and elsewhere (European Environment Agency, 2001). Line 1621: There is extensive evidence that quantitative as well as semi-quantitative assessments are vulnerable to subjective bias (see comments and refs above). Lines 1698-1704: A variety of conceptual models should be presented, exploring multiple scenarios including worst-case scenarios, since alternative concepts can give very different answers whilst all being consistent with the available data. The analysis should not be limited to sensitivity analysis (i.e. testing the effects of altering parameters within a single model) because conceptual model uncertainty is often greater.

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652	GeneWatch UK	GBR	3.6.2 Guidance to applicants	Line 1505: Add: Modelling of alternative scenarios under different assumptions and with a variety of conceptual models will also play a role in identifying potential long-term effects (e.g. Alphey et al., 2011, Medlock et al., 2009). Line 1526: The "verification" of a model is not the same as its "validation": verification consists of verifying that equations are solved correctly while validation consists of verifying that the equations implemented provide an acceptable representation of reality (e.g. Hemez & Doebling, 2001). Validation of computer models is essential, as highlighted elsewhere in the Guidance e.g. line 8444-847. Line 1546: The defining characteristics of the receiving environment and any conditions on these should also be outlined: for example GM daughterless carp would be expected to be released (if at all) only in areas where invasive carp were a problem. Line 1548: Add: Potential long-term adverse effects on health (e.g. due to altered transmission of pathogens, effects on human immunity etc.) and any resulting ethical requirements e.g. informed consent from persons who might be affected.
653	GeneWatch UK	GBR	3.6.1 Categories of long-term effects	Line 1464: There is an implication here that long-term effects do not have to be assessed before placing on the market: they do. Short-term effects may also differ from predicted or measured effects before placing on the market. The assessment is supposed to include both long-term and short-term effects, although uncertainties may be greater for long-term effects. Line 1474: Interactions with pathogens (including possible evolution of viruses) and human or animal immunity can also result in long-term effects on human or animal health. Line 1482: Williams & Jackson, 2007 is missing from the reference list.
654	GeneWatch UK	GBR	3.6 Long-term effects	Lines 1436-1440: This is a misunderstanding of Directive 2001/18/EC, as explained above. The comparison required in the Directive is with the "non-modified organism from which it is derived and its use under corresponding situations". There is no justification for releasing GM animals which are not present as non-GM animals in the same environment: in most cases these will be regarded as alien species and releases would not be allowed under other legislation/conventions. The release of GM pests, disease vectors and alien species has been proposed as part of a population suppression or population replacement approach (e.g. to reduce disease transmission): in this case the problem is not the absence of a non-GM comparator (as in its absence, the GMO would almost certainly not be authorised for release) but the absence of a "corresponding situation" in which the non-GM organism (which is harmful) would be released in similarly large numbers. In all these scenarios the GM organism is expected to be (or at least intended to be) less harmful than its non-GM comparator, but this does not mean that its release (which, for many applications, will greatly outnumber the wild population by e.g. a factor of ten or more for GM mosquitoes) will not be harmful. Assessment is therefore not of whether the GMO is more or less harmful than the non-GM organism (this is merely a step in the process): it must include an ecosystem assessment designed to fulfil the requirements of the Directive. There must also be a recognition that the ecosystem as a whole may change in ways that are not reversible (see comments on Lines 825-828).
655	GeneWatch UK	GBR	3.5.3 Statistical analysis	Line 1388: A new section is needed after this one: a section on Modelling. Modelling is mentioned in the Guidance on lines 77, 81, 782, 845 (which states that applicants deploying mathematical or other modelling techniques should seek to verify those models and justify explicitly their validation), 1105, 1106, 1146, 1225, 1522-1526, 1542, 1589-1592 (regarding uncertainty), 1603, 1625, 1629-1632 (assumptions), 1654-1656 (validity/uncertainty), 1689-1707 (choice of models, model structure effects, uncertainty and variability), lines 2183-2186 (fish), 2294-2296 (fish), 2516-2520 (pathogens in fish), 2745-2747 (modelling fish production systems), 3268-3271 (horizontal gene transfer in insects), 3891 and 3392-3394 and 4004 (insects and non-target organisms), 4106 (insect release management), 4123 (mosquito vector control dynamics: incorrectly described as validated models when they are not), 4294 (human immunity), 4522 (persistence of mammals and birds), 4529 (bioclimatic and species distribution models for mammals and birds), 4543 (inclusion of biotic and abiotic factors in models of mammals and birds), 4552, 4639-4671 (further requirements for modelling mammals and birds), 4677, 4837, 4998-5001, 5246-5250 and 5301 and 5307 and 5313-5317 and 5444-5446 (modelling of pathogens in mammals and birds), 5895 and 5946 (effects of GM mammals and birds on non-target organisms), 6134 and 6178 (management systems for mammals and birds). It would be helpful to readers if all the concepts referred to were outlined in one section. This would also help to ensure that principles outlined in one section (e.g. Lines 4639-4671) are applied to other sections (i.e. to insects and fish).

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656	GeneWatch UK	GBR	3.5.2 Principles of experimental design	Line 1219-1220: Mead (1990) is missing from the reference list. Line 1271: There are two Sundström et al. (2007) references in the reference list, these should be individually identifiable. Line 1353: The assumption that there are no interactions will not be valid in all cases. Ecosystem responses to large-scale open releases of GMOs may be non-linear.
657	GeneWatch UK	GBR	3.5.1 General Principles	Lines 1110-1118: This section should refer to the principle in paragraph (24) of EC (2001) i.e. that the introduction of GMOs should be carried out according to the 'step by step' principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken. Lines 1139-1140: Reference to EFSA (2010) should state whether this is 2010a,b,c or d. Presuming it is EFSA (2010c) it should be noted that this report was developed for application to GM plants. As noted in Section 3.2 (see also comments on this) the ERA of a GM animal would be more varied and complex, and encompasses a wider range of issues than the ERA of a GM plant or substance. Some of the issues have been highlighted in comments on Lines 386-391 (potential increase in a competitor species that is harmful), Lines 468 to 486 (potential harm to human health due to interaction with human immunity), and Lines 501-504 (potential for evolution of viruses in response to releases of GMOs), above. It is completely inadequate to base the assessment on the idea of 'limits of concern' as applied to plants and a basically toxicological approach: an ecosystem based approach is needed, otherwise steps 4,5 and 6 in Part D.1 of Annex II of Directive 2001/18/EC will not be adequately addressed. In the population suppression approach, for example, the primary impact on other species will not be through toxicity but through the fall in population of the target species (or potential fluctuations or even increases due to density-dependent effects, should the approach prove ineffective) combined with the response of the system of the whole (e.g. influx of the target species from surrounding areas, possible increases in competitors and reduction in predators, changes in the age or size structure of the population etc.). Addressing these issues would benefit from a new methodological report, since they are more complex than have been considered to date for plants. Multiple scenarios will need to be considered (see comments on Lines 501-504) and these may vary considerably in different receiving environments (for example, depending on the presence or absence of a particular agricultural pest). For disease vectors, the equivalent of clinical trials may be needed to assess impacts on human health (James et al., 2011): this lies way outside EFSA's expertise and certainly cannot be addressed merely by extrapolating from risk assessments for GM plants. There are also important ethical issues associated with conducting trials of releases of disease vectors, which are widely recognised to require informed consent (Macer, 2005). Lines 1151 and 1157: Heard et al., 2003 is missing from the reference list. Lines 1167-1173: Complex modelling will be needed to predict the interactions required to be assessed in part D.1 of Annex 2 of Directive 2001/18/EC (EC, 2001), steps 3, 4 and 5. Demonstrating the validity of these models must be part of the ERA.
658	GeneWatch UK	GBR	3.5 Experimental design and and statistics	Line 1133: Reference to EFSA (2011) should state whether this is 2011a or 2011b.
659	GeneWatch UK	GBR	3.4 The use of non-GM surrogates	Lines 1053-1107: This section should also emphasise the need to fully understand the baseline characteristics and behaviour of the target wild organism and non-target organisms in the receiving environment. For example, a full understanding of density-dependent effects on mosquito populations is critical to understanding responses to the release of GM insects in a population suppression approach (Juliano, 2007; Gould & Schliekelman, 2004; Walsh et al., 2011; Walsh et al., 2012; Barclay, 2001).

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660	GeneWatch UK	GBR	3.3.2 Choice of comparators for ERA of GM insects	Lines 1039-1048: Annex II of Directive 2001/18/EC, part B states that "identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations" (EC, 2001). For applications involving pests this poses a problem with a lack of "corresponding situations" since mass releases of non-GM mosquitoes or agricultural pests would not be contemplated. As suggested elsewhere in this Guidance, for population suppression one approach might involve a comparison with the Sterile Insect Technique (SIT). Comparisons with wild populations should also certainly be made. There is no requirement in Directive 2001/18/EC for a comparison with other management techniques (e.g. insecticides) although the impact of altered management techniques must be considered. GM insects are likely to be released as part of an Integrated Pest Management (IPM) programme which will include continued use of insecticides and other control methods: assessment of any changes to this management regime falls under step 8 of the nine step process, not under the selection of comparators. Release programmes run by authorities may require a Strategic Environmental Assessment, which involves considering alternatives (EC, 2001b), but this does not alter the need to produce an ERA to meet the requirements of 2001/18/EC. Multiple alternative management approaches are likely to be available and used in complex combinations in different locations and will not be limited to the use of insecticides alone (e.g. agro-ecological approaches to controlling pests; mosquito control programmes including public health approaches to reducing breeding sites and early surveillance for disease). Any comparison of GMO releases with alternatives would need to consider efficacy of the releases as well as risks and how the system might change with time e.g. as resistance develops. Lines 1049-1050: The implication that a GM pollinator would replace a non-GM pollinator of a different species is extremely worrying. The Guidance needs to be clear under what circumstances release of a different species of pollinator might be allowed (taking account of plant pest regulations and other relevant legislation). The strain must also be considered (see comments on lines 867-877). Annex II of Directive 2001/18/EC, part B states clearly that "identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations" (EC, 2001). There is no suggestion that a GM species can be used to replace a non-GM organism of a different species. Line 1052: A section on choice of comparators for ERA of GM mammals and birds is missing. This should also include guidance on comparators for the population suppression approach (the theoretical example of the "sterile" rabbit).
661	GeneWatch UK	GBR	3.3.1 Choice of comparators for ERA of GM fish	Lines 984-985: This section should recognise that some proposed applications involve population suppression of invasive fish species through the release of GM fish that mate with the wild ones and limit future reproduction. A specific proposed application is to produce GM carp that only produce male offspring and hence crash the population (Nowak, 2002; Thresher, 2008). Although this Australian project has recently lost funding (ABC, 2012); a different transgenic approach to producing all male fish and other animals has been patented recently (Aquabounty, 2011). Population suppression approaches need to be treated consistently in this Guidance, including in the insects and mammals and birds sections (the theoretical example of the "sterile" rabbit). These proposed applications could have very significant impacts on ecosystems since population suppression may be partial or temporary and give rise to complex interactions with competitors, predators, prey, symbiots, pathogens and humans. It is unclear to the reader whether the release of GM invasive species as part of a population suppression approach is consistent with existing legislation (since the release of the non-GM animals in such cases would normally be inconceivable) and, if so, how such applications would be assessed.
662	GeneWatch UK	GBR	3.3 Choice of comparators	Lines 945-949: This paragraph again makes no sense for population suppression approaches (as explained in comments above). Even where there is a non-GM version of a pest in the environment, assessing the environmental impacts of large scale releases of the GM version do not depend on a comparison between the GM and non-GM animal, because large scale releases of the non-GM pest would certainly not be allowed. The overall environmental consequences of the release must be assessed. The comparison between the non-GM and GM animal is only one aspect of this. The aspects which must be assessed are listed in part D.1 of Annex 2 of Directive 2001/18/EC. This is the starting point, not the comparative approach, which is merely one aspect of the assessment.

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663	GeneWatch UK	GBR	3.3 Choice of comparators	Line 854: The comparative approach is only one aspect of the assessment, as outlined in Directive 2001/18/EC and section 2.2 (see also the comments on that section). There will be no comparable use, for example, of non-GM mosquitoes or agricultural pests which would not be released in their millions into the environment because they are harmful organisms. There may of course be some potential to make a comparison with the Sterile Insect Technique (SIT) but there are important differences which will need to be considered as part of the assessment (see comments on insects section, below). The impacts of large-scale releases of GM insects for example are not predictable from a straightforward comparison between the GM and non-GM insect (see comments above on e.g. potential for increase in invasive competitor species, interactions with human immunity leading to more serious cases of disease, evolution of viruses). Lines 867-877: An important issue missing here is that different strains of the same species (e.g. a mosquito or agricultural pest) can vary significantly in their ability to transmit diseases (Aitken et al., 1997; Bonizzini et al., 2012; De Oliveira et al., 2003; Lima & Scarpassa, 2009; Scarpassa et al. 2008; Tabachnick et al., 1985; Van Den Hurk et al., 2011) and their resistance to insecticides (Martins et al., 2009, Ocampo & Wesson, 2004). This raises concerns about how introgression may effect both persistence and disease transmission (GeneWatch UK, 2012). Release of non-native strains will not be compatible with plant pest regulations, as highlighted by Oxitec's failed attempt to release a North American strain of GM diamond-back moth in the UK under contained use regulations (on the spurious claimed grounds that the genetic trait amounted to biological containment) (Oxitec 2011b; ACRE, 2011; HSE, 2011a&b; DEFRA, 2012; FERA, 2012). This issue has not been fully resolved since backcrossing the North American GM strain with a native strain will still not make the strain identical to a native one. In the case of disease vectors, such problems are exacerbated by the fact that disease transmission characteristics may vary significantly between strains and more than one strain may exist in the EU. Using strains that are different from the background strain (in a particular area) risks introducing new diseases to that area. Lines 888-903: It is unclear why EFSA is considering recommending the release of GM fish or insects into areas where no conventional counterpart exists. Re-interpreting Directive 2001/18/EC to allow such releases would appear to be stepping even further outside its remit than it already has. Further, such releases are unlikely to be compatible with other legislation, such as plant pest regulations. Lines 904-908 recognise that releasing a GM species into a receiving environment where it does not currently exist would amount to introducing an alien species but fails to mention any of the legislation or conventions whichwould prevent such introductions. Lines 908 to 914 amount to a misreading of Directive 2001/18/EC: the Directive is clear that effects such as interactions with other species must be considered: the difference between the GM and non-GM animal are only a part of this assessment as discussed extensively above. Lines 915-924 appear to be a correct interpretation.
664	GeneWatch UK	GBR	3.2 Experimental environment	Line 803: Add: Many animals are also vectors for existing pathogens and potential future reservoirs for new viruses to develop that may be transferred from animals to humans. This introduces a new level of complexity because transport and evolution of viruses, including their interaction with human and animal hosts becomes an important part of the risk assessment process. Lines 808-810: Add humans. Lines 825-828: The potential for irreversible effects (due to hysteresis) to occur even if the GMO is removed from the environment should also be considered: for example, ecological replacement by a more invasive competitor during the use of a population suppression approach; the evolution of a more virulent virus due to the release of GM virus-resistant mosquitoes or birds. Again, the Guidance is too focused on the idea of "exposure" (as if a toxicological assessment were being conducted and removing the exposure would remove the problem), rather than an ecosystem approach. Line 834: The presence of humans and pathogens must also be considered. Line 849: Add: Interactions with humans should be limited until potential adverse effects of the GMO and its behaviour and interactions in the environment are fully understood. Releases may be premature if the baseline receiving environment has not been sufficiently characterised or understood.
665	GeneWatch UK	GBR	3.1.3 Selection of the relevant receiving	Lines 782-788: Modelling will be required not only for persistence and invasiveness, but also to predict impacts on other species and diseases.

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			environments	
666	GeneWatch UK	GBR	3.1.3 Selection of the relevant receiving environments	Lines 733-734. This paragraph should be clear that it is not advocating open release experiments in the highest risk areas: or is it? See comments on lines 248-250. In general, the Guidance fails to recognise that many proposals for releases (at least for a population suppression approach) will be for invasive species, on the grounds that releasing the GM organism will reduce the numbers of an undesired non-GM organism (a pest, disease vector or invasive species). In such cases there may be no receiving environments where the risks are considered acceptable or there may be some restricted environments, with characteristics such as: a severe problem due to the pest, lack of alternatives to tackle it, and expected low adverse impacts on non-target organisms and human health. The Guidance seems to imply that authorisations will be granted for placing on the market across the whole of the EU, which is not remotely realistic given the potential risks of releasing GM insects (mosquitoes or plant pests) or fish in the wrong areas. Insufficient attention has also been paid to how spread into non-authorised environments will be avoided. For example, Oxitec lists more than 50 species of insects it wants to genetically modify in its patent (Oxitec, 2011a): how will these be restricted to areas where the target pest is actually a problem and not allowed to spread to other receiving environments? The same problems apply to other highly mobile species, such as GM salmon or GM bees. Lines 737-739: Again, this appears to advocate causing potentially irreversible harm to non-target organisms in order to conduct experiments on safety: the need for a step-by-step approach, focusing on contained experiments in the first instance, should be emphasised. This is particularly important where there are potential adverse impacts on human health: for example, contained trials and trials in non-inhabited areas should be prioritised over trials in inhabited areas. For example the risk identified in comments on lines 468-486 is associated with open releases of GM mosquitoes (vectors for dengue) in inhabited areas where dengue is endemic: these should be the last places where tests are conducted if the efficacy of the technology is uncertain. For mosquitoes, to answer questions about impact in nature requires field experiments to manipulate species densities under realistic conditions; to answer questions about biological details requires more-complex experiments to manipulate other factors in addition to population density; whilst some questions about biological details can be answered using experiments under less realistic, but more precisely controlled, laboratory conditions (Juliano, 2009). However, important questions about e.g. competition between species and the effects ecological interactions can be assessed in the first instance without releasing GM insects: this helps to establish a baseline level of understanding for the step-by-step approach as required by paragraph (24) of Directive 2009/18/EC (EC, 2001). Lines 762-767: A major proposed application is to combine GM agricultural pests (Oxitec's RIDL technology) with GM crops (pest-resistant Bt crops) in an attempt to tackle the growing problem of the emergence and spread of resistant pests (Alphey et al., 2007; Alphey et al. 2009; Oxitec, 2011b). The Guidance should therefore refer not only to combinations of GM animals, but also combinations of GM animals with GM plants. Taking into account all GMOs already in the environment (not just other GM animals) is a requirement of Directive 2001/18/EC Annex II (Part B, General Principles). Line 781: Add: Human populations, including relevant characteristics e.g. age, disease status.
667	GeneWatch UK	GBR	3.1.2 Identification and characterization of the receiving environments	Lines 700-701: Interactions with humans should be added. Lines 713-714: Pests and pathogens associated with the GM animal and its non-GM comparators and its competitors need to be considered, for the reasons outlined in comments on lines 386-391 above. Lines 722: Add: Including interactions with humans. Lines 726-727: Table 2; Pests (e.g. pathogens and parasites) and diseases should be added to the 2nd column (as well as the first), under "Biotic and abiotic ecosystem sub-factors interacting with the GM animal".
668	GeneWatch UK	GBR	3.1.1 Definition of receiving environments	Lines 648-657: It would be helpful to consider both intended and unintended environments. Some GMOs, especially fish, insects, some birds and mammals (e.g. rats) and eggs or sperm of any species, may spread easily outside the intended receiving environment, either inadvertently through transport on clothing or in ships or tyres; or through poorly regulated marketing (e.g. sale of GM bull sperm). Impacts of accidental releases will have to consider potential impacts outside the intended receiving environment. For example, GM salmon produced by the company Aquabounty are intended for production in on-land facilities, but might escape via water outflows and/or appear in EU waters as a result of poorly controlled marketing or shipment of eggs. The potential impact on wild salmon populations will therefore need to be assessed.

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669	GeneWatch UK	GBR	3.1 Receiving environments	Lines 640-646: The specific information required by Annex III A of Directive 2001/18/EC (EC, 2001) should be listed here.
670	GeneWatch UK	GBR	2.3 Structural overview of this Guidance Document	Lines 619 to 623: As noted in earlier comments, these specific areas of risk should have been listed much earlier in the document and a process should have been adopted which encompassed all of them from the outset (rather than being restricted by the concept of "exposure assessment"). As noted in comments on the contents, specific sections on Pathogens, infections and diseases; Abiotic interactions; and Impact on non-GM animal health and welfare have been omitted from the insects section. There is no justification for issuing a consultation with these sections missing: further consultation is likely to be needed once they have been included.
671	GeneWatch UK	GBR	2.2 Information to identify potential unintended effects	Line 2.2 Add: In addition, Directive 2001/18/EC requires effects due to direct and indirect interactions between the GMO and target and non-target organisms (including competitors, prey, hosts, symbiots, predators, parasites and pathogens) and human health to be characterised. Line 590: Add: biotic interactions include those between the GMO and target and non-target organisms (including competitors, prey, hosts, symbiots, predators, parasites and pathogens) and human health. Line 615: Information on the GMO itself and its comparator is only a small part of the information required to meet the regulatory requirements: the information listed here is insufficient to fulfil the claimed purpose of the heading i.e. to identify potential unintended effects. Add: for both types of applications information on the intended release or use including its scale; the potential receiving environment; and the interaction between these is also required (Annex II, EC, 2001). The Directive's requirements in Annex IIIA should also be cited here. For example, information required on the receiving environment includes that listed in Annex IIIA of Directive 2001/18/EC: 1. geographical location and grid reference of the site(s); 2. physical or biological proximity to humans and other significant biota, 3. proximity to significant biotopes, protected areas, or drinking water supplies, 4. climatic characteristics of the region(s) likely to be affected, 5. geographical, geological and pedological characteristics, 6. flora and fauna, including crops, livestock and migratory species, 7. description of target and non-target ecosystems likely to be affected, 8. a comparison of the natural habitat of the recipient organism with the proposed site(s) of release, 9. any known planned developments or changes in land use in the region which could influence the environmental impact of the release.
672	GeneWatch UK	GBR	2.1.5 Step 5: Risk management strategies	Line 518: Infertility can reduce direct risks (e.g. exposure to any toxin in the GM animal) but methods of limiting reproduction are also envisaged as a means to make a major change to ecosystems e.g. by releasing large numbers of GM insects with a conditional lethality trait (Oxitec's RIDL mosquitoes and agricultural pests) or by releasing GM invasive species e.g. carp (Thresher, 2008) to breed with and reduce wild populations. This method could potentially be applied large numbers of other species (AquaBounty, 2011). This paragraph incorrectly implies that infertility is only a method of reducing risks: in reality it may reduce some direct risks related to survival of the GM organism, but introduce or increase other indirect risks such as the potential to crash populations of some species, with knock-on effects on the rest of the ecosystem. The Guidance is generally poor on recognising the risks associated with such population suppression approaches, which might be applied in future to insects, fish, mammals and birds. Directive 2001/18/EC requires that these risks due to ecosystem interactions are assessed. Line 527: There is no such thing as GM sterile mosquitoes: this term should be avoided. Oxitec's GM mosquitoes have a conditional lethality trait: this is conditional because it relies on tetracycline as a chemical switch to allow breeding in the lab; partial because it does not have full penetrance; and late-acting i.e. the insects are not sterile but mate and reproduce with most dying at the late larval stage (in the absence of tetracycline) (Phuc et al., 2007). Many applications are also female-killing only (i.e. sex-specific). The use of the term sterile is misleading because it implies there is no exposure to female biting GM mosquitoes or prospect of survival and breeding of the GM mosquitoes in the environment, which is incorrect. Line 545: It is questionable whether the applicant is best placed to devise its own worst-case scenarios when its aim is to get its product on the market. Alternative conceptual models, which might identify unexpected risks (e.g. Medlock et al., 2009) require time and resources to develop, which requires independent funding. It is not clear where such capacity and expertise currently resides: clearly not with EFSA.

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673	GeneWatch UK	GBR	2.1.4 Step 4: Risk characterisation	Lines 496-500 provide an inadequate characterisation of uncertainties. Characterising the potential direct and indirect interactions between the GMO and target and non-target organisms (including competitors, prey, hosts, symbiots, predators, parasites and pathogens) and human health (as required by Directive 2001/18/EC) is a potentially mammoth task for mobile organisms such as insects and fish, and mobile mammals (such as rats or rabbits) and birds. It is inconceivable that such a task can be based merely on "extrapolations": it is likely that complex environmental models will be needed, with multiple alternative assumptions explored in alternative scenarios and a need for a thorough understanding of natural ecosystems to define concepts (i.e. write the model equations) and determine input parameters (see comments on Section 3). Further research will then be needed to validate the models i.e. to establish that they have sufficient predictive value to be fit for purpose. The use of unvalidated models that are not fit for purpose would likely give rise to wrong predictions with potential adverse consequences. Lines 501-504: Multiple scenarios will need to be explored, including more than one worst-case scenario. This is because different model assumptions will give very different answers. For example, dengue virulence in mosquitoes can be selected for by release mosquitoes genetically-modified to block transmission, reduce biting, or increase mortality, but the evolutionary trade-offs that lead to the virus become more virulent as a result of the GM mosquito releases depend on the assumptions in the model (Medlock et al., 2009). The potential for such adverse impacts on human health would need to be ruled out before any releases were allowed (on the ethical basis of "do no harm"), but doing so would be a major task due to the extent of the uncertainty. This paragraph again focuses misleadingly on "level of exposure" which is only one part of problem formulation if major risks are indirect or result from interactions rather than direct exposure to the GMO. Line 506: "Exposure characterisation" is too limited. Add: characterisation of interactions between the GMO and target and non-target organisms (including competitors, prey, hosts, symbiots, predators, parasites and pathogens) and human health (as required by Directive 2001/18/EC).
674	GeneWatch UK	GBR	2.1.3 Step 3: Exposure characterisation	Line 468: Change "Exposure characterisation" to "Characterisation of potential impacts". Lines 468-486: As noted in comments on lines 386-396 the concept of exposure characterisation is too narrow to capture the wide range of potential adverse effects on the environment and human and animal health associated with significant changes to ecosystems: a term such as "Characterisation of potential impacts" would be better. For example, releases of GM mosquitoes in a population suppression approach may be only partially or temporarily effective at suppressing populations. In the case of dengue vectors, a partial reduction in mosquito numbers in dengue-endemic areas can lead to an increase in cases of dengue hemorrhagic fever (the more severe and often fatal form of the disease) (Thammapalo et al., 2008; Nagao & Koelle, 2008). Such potential negative impacts on human health are not captured in a methodology which focuses on exposure to the GM organism: they are not caused by exposure to the GM organism but by the complex interactions between the release programme for the GMO, ecosystems, humans and disease. Annex II of Directive 2001/18/EC (EC, 2001) is very clear that such interactions must be considered (see list in D.1, especially points 4, 5 and 6), but the process adopted here is too narrow to do this. Exposure characterisation is only a part of the characterisation of potential impacts. This issue is recognised to some extent in Section 3.2 but this recognition of complexity is not reflected here
675	GeneWatch UK	GBR	2.1.2 Step 2: Hazard characterisation	Line 457: Should also refer to harm to human and animal health. Line 459: Should refer to potential adverse impacts on human and animal health, not just on the environment.
676	GeneWatch UK	GBR	2.1 Different steps of the Environmental Risk Assessment	Lines 418 to 440: This section seems to be cut-and-pasted from a similar approach used for plants where, for example, exposure of non-target organisms to toxins from Bt plants is one of the main considerations. These steps are a poor fit to deliberate or accidental releases of large numbers of GM fish, insects, birds or mammals, which may disperse and mate with wild species and potentially cause adverse effects via interactions with ecosystems. The ultimate objective of this list should be to enable conclusions to be reached regarding all the potential impacts from the release of GMOs other than higher plants identified in part D.1 of Annex II of Directive 2001/18/EC (EC, 2001). Line 423: Annex II of Directive 2001/18/EC (EC, 2001) requires identification of the characteristics of GMO and releases (C.1), including the intended release or use including its scale; the potential receiving environment; and the interaction between these. By omitting the characteristics of the receiving environment and release programme from consideration here, the Guidance risks missing important aspects of the analysis. For example, a population suppression approach for a particular pest, using releases of partially/conditionally sterile GM fish or insects would almost certainly not be considered in receiving environments were the pest was not already established. Further, many of the risks would depend on interactions between multiple species, rather than on some direct characteristic (such as toxicity) of the GMO itself. Line 427: The use of the term "exposure pathways" is too restrictive as it does not identify the potential harms due to ecosystem interactions identified in part D.1 of Annex II of Directive 2001/18/EC (EC, 2001). See comment on lines 386-391.

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				Lines 429-440: These steps are over-simplistic for many of the relevant applications and take no account of the potential hazards of conducting the experiments to measure the envisaged endpoints. See comments on lines 248-250. Annex II of Directive 2001/18/EC (EC, 2001) requires the ERA to assist in drawing conclusions on, inter alia, potential immediate and/or delayed environmental impact on interactions affecting levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens. GM fish and insects will not sit still in a field but swim or fly and mate. Predicting the consequences of releases will require a thorough understanding of natural ecosystems (including humans and viruses) to develop and validate computer models of such systems. Taking a precautionary approach (as required by the Directive) means that it will not be good enough simply to set endpoints, conduct releases, and wait see if the predictions are correct. A pre-requisite to conducting any releases must be a good understanding of the natural system and how it might be disrupted by the introduction of the GMO.
677	GeneWatch UK	GBR	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 412-417: This paragraph underpins a fundamental misconception that permeates this entire document i.e. that it is the difference between the GM animal and its wild counterpart that matters ("a minimum level of difference between the GM animal and its conventional counterpart that may lead to harm"). This may be relevant for some applications (e.g. replacing a GM cow with a non-GM cow), but many applications for open release are likely to involve GM animals which would not normally be allowed to be released into the wild and which are intended to alter entire ecosystems (not just to replace non-GM animals in a particular production system with GM animals). Examples include a wide variety of species intended to be used in the population suppression approach to reduce numbers of disease vectors, plant pests and invasive species: e.g. GM mosquitoes (Phuc et al., 2007); GM agricultural pests (Morrison & Alphey, 2012); GM fish, crustacea, molluscs and amphibians (Aquabounty, 2011; Nowak, 2002; Thresher, 2008) and perhaps mammals (the theoretical example of 'sterile' GM rabbits given in this document, but perhaps also other pest species such as rats). These animals will not in general be sterile but have a genetically engineered form of conditional lethality: i.e. sterility may be partial, late-acting and conditional (because a system which over-rides lethality is needed to breed the animals in the lab). Many insect applications are also female-killing only (i.e. partial, late-acting, conditional and sex-specific). Other potential applications include insects or other animals with altered disease transmission properties; non-native species of bees engineered to be pest- or pesticide-resistant or to have other supposedly useful characteristics (e.g. pollination). With many such applications it is not the difference between the GM and non-GM animal that causes the potential harm but the complex response of the entire ecosystem (including both unintended survival and spread of the GM organism and knock-on effects such fluctuations in species numbers or increased transmission of viruses). For example, extinction of one species can have knock on effects on other species (Sanders & van Veen, 2012). It is vital that consideration of any such releases takes account of (1) existing legislation on the release of invasive species (e.g. plant pest regulations) and disease vectors; (2) the need for an ecosystem-based approach to any assessment, which recognises that a dynamic complex of plant, animal and micro-organism communities and their non-living environment interacting as a functional unit (CBD, undated).
678	GeneWatch UK	GBR	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 386-391: The phrase "exposure pathways" makes sense in toxicology but becomes meaningless in complex ecosystems. Directive 2001/18/EC (EC, 2001) requires consideration of complex interactions between the GMO, predators, prey, competitors, pathogens, humans etc. (see comment on line 338). This requires an ecosystem approach (CBD, undated) which cannot be reduced to a simple question of exposures. For example, release of GM Aedes aegypti mosquitoes, a vector for dengue and other viruses, can have complex effects on populations of Aedes albopictus mosquitoes (also a vector of dengue and other viruses), including possible increases in the population of the latter, due to reduced competition between larvae (Bonsall et al., 2010). This poses a potential risk, since Aedes albopictus is in invasive species which can cause dengue epidemics (Beech et al., 2009; GeneWatch UK, 2012). However, the term "exposure pathway" is not really meaningful to encapsulate this risk: what does the term exposure mean in this scenario? Possible pests and pathogens associated with the ecosystem as a whole (not just the GM animal) need to be considered, as for example in the scenario described a disease carried by a competitor species (rather than the GMO) might increase as a result of the releases and thus cause adverse impacts on human health.
679	GeneWatch UK	GBR	2.1.1 Step 1: Problem formulation (including identification of hazard and exposure pathways)	Lines 357-357: This section should refer at the outset to the need for an ecosystem-based approach (CBD, undated). Lines 360-361: Should also refer to health-related legislation since many relevant organisms are vectors of human and animal diseases. Line 362 and 370-372: Table 1 is deficient in many respects. Examples of major omissions include: (1) the omission of the International Plant Protection Convention (IPCC) and related EU legislation (EC, 2000); (2) the Helsinki Declaration, which requires informed consent to medical experiments, and the Oviedo Convention: both relevant to releases of GM disease vectors (Macer, 2003; Macer, 2005). Oxitec has also run into difficulties with its plans for open releases of GM diamond-back moths in the UK, due to its failure to consider plant pest regulations (HSE, 2011a&b; DEFRA, 2012; FERA, 2012). Many relevant conventions e.g. covering marine protection, are also omitted from Table 1, as are animal health requirements (e.g. EC, 2006). In the UK (as an example) the Health Protection Agency has as one of its functions to prevent the spread of infectious disease, and any programmes to control vectors of disease using GM approaches are likely to require scrutiny by it. Plans and programmes by public authorities to release large numbers of GM animals e.g. insects e.g. for population suppression across multiple farms or fields may require a Strategic Environmental Assessment (EC, 2001b)

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				Lines 363 to 369: It is not only the characteristics of the GM animal but the characteristics of the programme for its deliberate release (e.g. numbers, location) that can cause harm or adverse effects on human health or the environment. A GM animal may be less harmful than its wild counterpart (e.g. it may be partially sterile and less fit, and therefore less invasive) but still cause significant harm because (1) if it is a harmful organism (e.g. disease vector, invasive species) releasing a less-fit version may still cause harm; (2) the impacts of releases on ecosystems are intended to be significant (a large change to the population) and can have harmful knock-on effects (including increases in harmful competitors, or rebounds in numbers due to complex interactions). These concerns are in addition to any differences between the GM and non-GM organism that may in themselves be harmful. These issues are recognised in Annex II, part D.1 of Directive 2001/18/EC (EC, 2001) but not adequately covered here.
680	GeneWatch UK	GBR	2.1 Different steps of the Environmental Risk Assessment	Line 329: Should say: on the receiving environments and human health. Line 338: Should cite the conclusions required in the case of GMOs higher than plants (D.1) from Annex II of Directive 2001/18/EC (EC, 2001): 1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s). 2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s). 3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species. 4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable). 5. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts,symbionts, predators, parasites and pathogens. 6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s). 7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed. 8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s). 9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific techniques used for the management of the GMO where these are different from those used for non-GMOs. Lines 338: The proposed approach pays insufficient attention to points 4, 5 and 6 in part D.1 Annex II of Directive 2001/19/EC, cited above, which refer to direct and indirect interactions between the GMO and target and non-target organisms and humans, and effects which may be immediate or delayed. Addressing these issues requires an ecosystem-based approach (CBD, undated).
681	GeneWatch UK	GBR	2. Strategies for the ERA of GM animals	Line 304: Should also refer to the requirement for an ecosystem approach (CBD, undated). This is essential to consider the risks of deliberate or accidental releases. A comparative approach plays a role but is more important in the comparison of a single GM animal with a single non-GM animal and may not help to ascertain the risks of e.g. a large release of GM fish or insects. Line 307: Intended effects may include significant effects on ecosystems, such as a significant reduction in the population in the population of a particular pest species or disease vector (in population suppression approaches), or the replacement of a population (e.g. replacing a mosquito population with one which is a less effective vector of disease). Line 312-314: In the case of large-scale deliberate (or accidental) releases (e.g. of GM insects, fish), secondary effects may include altered populations of competitors, predators or prey and effects on human or animal immunity due to altered disease transmission. Longer-term effects can include development of resistance to the GM trait or evolution of viruses in response to changes in the disease vector.
682	GeneWatch UK	GBR	1. Scope of this Guidance Document	Lines 267-272 contd: Further, the population suppression approach involves the release of very large numbers of mostly male GM insects to mate with wild females: release ratios to date have been up to 54 GM mosquitoes to wild mosquitoes and production in Brazil is being scaled up to 2.5 million mosquitoes a week (PAT, 2012). If the population suppression strategy is applied to e.g. Mediterranean fruit flies (Ceratitis capitata) – one of the species on which Oxitec is working, and which it might wish to release in the EU – releases of millions of flies could contribute to the transfer of human pathogens from faeces to fruit (Sela et al., 2005). This aspect (increased ingestion of transferred pathogens), as well as ingestion of GM insects directly, is completely ignored in the EFSA Guidance (EFSA, 2012a) despite the claim here that ingestion risks have been dealt with there. Other proposed uses of population suppression (for fish, insects, crustacea, molluscs, amphibians or mammals) could also pose risks to the food chain; as could insects released for other purposes (e.g. pesticide-resistant or pest-resistant GM bees; disease-resistant mosquitoes). EFSA guidance on risk assessment of food and feed from genetically modified animals considers whether the GM animal may be more susceptible to pathogens, but ignores the potential for the releases of large numbers of GM pests (whether GM insects, fish or mammals e.g. carp, rats or the

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				theoretical 'sterile rabbit' included in the consultation) to spread pathogens: this is a result of the failure to adopt an ecosystem approach. It is difficult to understand why EFSA has focused much of this guidance on issues outside its remit and/or expertise whilst failing to provide any guidance on issues that are within its remit.
683	GeneWatch UK	GBR	1. Scope of this Guidance Document	Lines 267-272: In its previous consultation on risk assessment of food and feed from genetically modified animals EFSA stated explicitly that "Insects and other invertebrates were not taken into account, with the exception of honey bees that are used in agricultural practice" (EFSA, 2011). This statement was repeated in the final Guidance (EFSA, 2012a). In its response to the consultation, GeneWatch highlighted that GM insects and invertebrates (including GM bees) raised a whole range of additional issues which could not be properly considered in this document and required separate in-depth consideration (GeneWatch UK, 2011). Yet now, EFSA appears to be implying that accidental intake (ingestion) of GM insects not intended for food and feed is included under this guidance. This is an important issue because the ingestion route may be significant in many GM insect applications. For example, Oxitec's RIDL insects will give rise to very large numbers of GM insect eggs and larvae potentially entering the food chain, since the late-acting lethality system causes most of the offspring to die at the late larval stage (Phuc et al., 2007): this has already been a concern with Oxitec's proposal to release GM diamond back moths in the UK, because of concerns that GM eggs and larvae will contaminate food crops such as cabbages and broccoli (GeneWatch UK and GM Freeze, 2012; Spelman, 2012). Oxitec's GM olive flies contain a late-acting lethality trait which means that they are expected to die mostly at the pupal stage (Ant et al., 2012), when olive flies remain within the olive. Oxitec expects these dead pupae to be treated as an 'adventitious presence' under EU law (Ant et al., 2012) but it is hard to see this being either publicly acceptable or compatible with food safety legislation. Details are not yet published for Oxitec's GM tomato leaf borers (Morrison et al., 2011) but it is likely that dead GM larvae will also remain within the tomato fruit. Failure to consider food safety and trade issues for GM insects is a particularly important omission because international guidelines do not cover this either (Codex Alimentarius, 2008): this means there has been no discussion of the implications for consumers and international trade. These issues were highlighted in the expert report to EFSA (page 98) which expressly mentioned the prospect of food such as fruits being contaminated with GM eggs and larvae (Umweltbundesamt, 2012).
684	GeneWatch UK	GBR	1. Scope of this Guidance Document	Line 250: Transboundary notification requirements (EC, 2003) require the exporter to provide "A previous and existing risk assessment report consistent with Annex II of Directive 2001/18/EC". This Guidance should state explicitly whether or not it is intended to apply to these requirements. Oxitec's compliance with the transboundary notification requirements to date has been extremely poor (GeneWatch UK, 2012). Lines 250-252: Some aspects of traceability, labelling and co-existence are an essential part of risk management, see comments on lines 185-186. Risk management is repeatedly discussed in this document, as is post-market monitoring (which also requires traceability). Lines 259-263: Why are crustacea, molluscs, amphibians not included? (see comment on line 48). Why are issues included which fall outside EFSA's remit? (see comments on lines 195-211). Line 266: Why is the use of GM animals for production of pharmaceuticals excluded? Whilst EMEA may approve pharmaceutical products from GM animals it does not consider environmental impacts (which still require an Environmental Risk Assessment) or accidental impacts on the food chain. The guidance should clarify whether all GM animal products e.g. low-lactose or high omega-3 or human proteins in cows' milk will require approval by EMEA, and clarify more specifically which traits could as "pharmaceutical production" for the purposes of this guidance (e.g. where is the line drawn between nutraceuticals and pharmaceuticals?). If some or all of these applications are to be included, re-consultation is necessary so that consultees know what they are being consulted about.
685	GeneWatch UK	GBR	1. Scope of this Guidance Document	Lines 248-250: The guidance is full of contradictory information regarding the distinction between commercial and experimental uses: this needs to be clarified with reference to the requirements of Directive 2001/18/EC (EC, 2001). For example, lines 1226-1229 imply that open release experiments will not be allowed prior to commercial approval; whereas line 5859 implies that open field studies should be undertaken for mammals and birds, provided the potential environmental risks of such studies are considered. A whole Section (3.5) discusses experimental studies and Section 3.4 emphasises the use of GM surrogates in order to avoid open experiments with the GM animal itself. Yet, since no guidance is envisaged for experimental purposes it is unclear how these environmental risks will be considered and taken into account when applications for open releases for experimental purposes are made. Reference should be made to the 'step by step' principle in paragraph (24) of EC (2001) which requires containment to be reduced only gradually step-by-step "only if the evaluation of earlier steps in terms of the protection of human health and the environment allows the next step to be taken". Member states should be aware that large numbers of animals could potentially be released as part of experiments: open release experiments using Oxitec's GM mosquitoes in Brazil have to date used 10 million GM mosquitoes, and larger numbers are planned. It would be helpful to have clarified here whether such releases would count as placing on the market in the EU: Directive 2001/18/C seems to suggest that they would since "placing on the market means making available to third parties, whether in return for payment or free of

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				charge" (Article 2, paragraph (4), EC, 2001). If so, the claim that "release for experimental purposes" is not covered by this Guidance may need to be revised, since some experiments may count as placing on the market. It is worth noting that Part B notifications (deliberate release for any other purpose than for placing on the market) under Directive 2001/18/EC are decided by Member States but insects, fish and many mammal or bird species may become widely dispersed and potentially move into the territory of another Member State as the result of an experimental release. In view of Oxitec's repeated attempts to claim that its RIDL technology is equivalent to "biological containment" (see comments on line 176) it is perhaps worth reiterating here that the requirement for regulation as a contained use application i.e. that stringent containment limits contact with the population and the environment (Paragraph (4), Article 2, EC, 2001) is not met by Oxitec's RIDL insects, nor conceivably by any other population suppression approach that might be attempted using GMOs (for insects, fish, birds or mammals). Mating with a wild species cannot be regarded as limited contact.
686	GeneWatch UK	GBR	1. Scope of this Guidance Document	Lines 239-241: The mind-set of the entire document appears to be based on extending an approach applied to GM plants to GM animals. The underlying concept appears to be that GM animals may replace non-GM animals in specific production systems by individual commercial producers; and that the aim of the risk assessment is to ensure that these do not introduce harms above certain levels (to be determined by the applicant). However, the broadening of the remit of the guidance (see comments on Terms of Reference) means this may not be appropriate to many of the potential applications. For example, large scale experimental releases of Oxitec's GM fluorescent bollworms have already taken place in the USA: these are not constrained to a single farm or production system. Releases of Oxitec's GM mosquitoes (Aedes aegypti) are also now taking place on a large scale in Brazil. At what point do these types of applications count as "placing on the market" (the releases are being conducted via third parties in Brazil)? How will transboundary impacts be dealt with? How will potentially very different impacts in different receiving environments be dealt with (for example, releasing a species of GM insect pest in an area where it is not established may risk it becoming established there)? Similar population suppression approaches may be applied to fish, molluscs, amphibians and other animals in future (Aquabounty, 2011) yet the Guidance is largely silent on the issues raised.
687	GeneWatch UK	GBR	Assessment	Lines 231-236: Numerous important requirements such as plant pest regulations are omitted here (see also comments on Section 2.2.1).
688	GeneWatch UK	GBR	Terms of reference as provided by the European Commission and EFSA	Lines 195-211: It is hard to understand why the EC has requested much of this report which falls so far outside EFSA's food safety role. It is clear that the biotech industry has exerted pressure to adopt guidelines which would allow the introduction of GM fish and insects to the EU market (see comment on Line 176) but EFSA's focus is on risks to the food chain (EC, 2002). Whilst the original remit was to build on work done in the context of Codex Alimentarius (i.e. covering food safety standards) the later revisions to the mandate for the report extend way beyond this e.g. to population suppression techniques intended to engineer whole ecosystems, or alter disease transmission or pollination. The release of GM mosquitoes in an attempt to alter disease transmission, for example, has nothing to do with the free movement of food and feed within the EU. Although some aspects (e.g. potential contamination of the food chain with GM eggs, larvae or adult insects) do fall within EFSA remit, these aspects have been deliberately ignored and explicitly excluded from any form of consultation: see comments on lines 185-186 (traceability and labelling) and 267-272 (risks of ingestion of GM insects). Lines 228-230: Whilst non-food/feed uses may clearly impact on the food chain in various ways, many impacts may not be on the food chain but on ecosystems, disease transmission, pollination etc. EFSA's mandate (EC, 2002) states that in order to avoid duplicated scientific assessments and related scientific opinions on genetically modified organisms (GMOs), the Authority should also provide scientific opinions on products other than food and feed relating to GMOs as defined by Directive 2001/18/EC (1) and without prejudice to the procedures established therein. However, the entire mandate is predicated on the basis that EFSA exists in order to ensure the effective operation of the internal market for food and feed. The link between some proposed applications (especially the release of GM disease vectors and pets) and EFSA's remit is tenuous at best. Further, EFSA has not established expertise in many of the relevant areas.
689	GeneWatch UK	GBR	Background as provided by the European Commission and EFSA	Lines 185-186: Issues relating to traceability, labelling and co-existence are a key element of risk management. For example, in the US, the fact that large-scale releases of Oxitec's GM fluorescent bollworms are incompatible with organic standards appears to have led to this programme being halted: this would suggest that open releases which are compatible with co-existence rules are unlikely to be achievable in Europe (Reeves et al., 2012). Traceability of food crops containing GM insect eggs and GM larvae is also critical to monitoring human health effects and to preventing dispersal into receiving environments where releases have not been authorised. Line 187: Whilst it is correct to state that ethical and socio-economic issues are outside EFSA's remit, the issuing of draft Guidance before such issues are addressed is premature. The production of GM mammals, including pets and farm animals, raises many important ethical issues (GeneWatch UK, 2002) and much of the harm to animal welfare (e.g. aborted foetuses) is caused at the production stage of GM mammals. For example, in the case of production of transgenic pigs with increased levels of omega-3 fats in their meat, a total of 1,633 reconstructed embryos were transferred into 14 pigs; 12 early pregnancies were established, and five of them went to term leading to 12 (ten alive and two dead) male piglets being born by either caesarean section or natural delivery (Lai et al., 2006). Ethical concerns about this process have been completely ignored. In the

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				case of GM fish, the North Atlantic Salmon Conservation Organisation (NASCO) states in the Williamsburg Declaration: "In view of the current lack of scientific knowledge on the impact of transgenic salmonids on wild salmon stocks, the use of transgenic salmonids should be considered a high-risk activity. There should be a strong presumption against any such use" (NASCO, 2006). There is strong opposition to the introduction of GM fish from fishing organisations and producers in the EU. Yet EFSA's starting point seems to be that the production and deliberate release of GM animals is ethical and acceptable. Oxitec (which is acting as an advisor to the Working Group on Insects) has already been strongly criticised for failing to seek informed consent for its releases of GM mosquitoes overseas (Enserink, 2010) and it is widely recognised that informed consent is needed for releases of genetically modified disease vector species (Macer, 2003; Macer, 2005). Yet the Guidance does not even mention informed consent as an issue that must be addressed. Food safety, consumer acceptability and trade issues associated with the use of GM agricultural pests have also been ignored (see comments on lines 267-272) as have the implications for plant pest control regulations.
690	GeneWatch UK	GBR	Background as provided by the European Commission and EFSA	Line 176 contd: Oxitec's influence on the draft Guidance has clearly been substantive. "Sterile" GM insects (a term favoured by Oxitec in its PR materials) have been referred to more than 20 times, despite the fact that this term is misleading (Reeves et al., 2012): Oxitec's GM insects contain a lethality trait that is partial (i.e. not fully penetrant), conditional (dependent on the absence of tetracycline which is used as a chemical switch to allow breeding in the lab) and late-acting (normally at the larval stage) and many applications are female-killing only (there is also a flightless-female mosquito): further, resistance to the trait may develop over time. Transgenic "sterile" insects are referred to in Guidance on "Confined Field Release" of transgenic arthropods issued by the North American Plant Protection Organisation (NAPPO, 2007a), written with assistance from Oxitec (NAPPO, 2007b). The NAPPO guidance and the use of the term "sterile" appears to be part of an attempt by Oxitec to claim that its insects have "biological containment" and therefore that open releases of the insects should not count as open releases of GMOs for the purpose of regulation (despite the facts that they mate with wild females; and that some of the transgenic insects will survive). Oxitec has also made a failed attempt to release a US strain of GM diamond-back moth in the UK under contained use regulations on the spurious claimed grounds that the genetic trait amounted to biological containment (Oxitec 2011b; ACRE, 2011; HSE, 2011a&b; DEFRA, 2012; FERA, 2012). The concept that many risks are only or mainly relevant to replacement strategies and not to Oxitec's population suppression approach is also reiterated in this draft Guidance more than 20 times, rarely with any scientific justification. Only 13 scientific references are mentioned in the GM insects section (and six of these relate only to horizontal gene transfer). In lines 4092-4094 a sentence has been inserted which completely changes EFSA's remit and the purpose of Environmental Risk Assessment (presumably this sentence was added at Oxitec/Syngenta's request). It is surprising that other members of EFSA's GM insects working group (such as the Vice Chair of the EFSA GMO panel, Patrick Du Jardin) did not seek to prevent this attempt to change EFSA's remit through the back door.
691	GeneWatch UK	GBR	Background as provided by the European Commission and EFSA	Line 176: The establishment of the working groups did not follow an open and transparent process and the Insects Working Group is unduly influenced by Oxitec (see comments on Line 2). Mike Bonsall, a member of the working group who is one of Oxitec's collaborators "admitted he was an author of the GM animal draft safety guidelines. He confirmed there had been pressure from the biotech industry to get the rules written so that work on the safety case could begin" (Clover, 2012). There are issues regarding public trust in EFSA being so closely associated with a company that has been widely criticised for not following existing regulations and ethical requirements. Oxitec has failed to correctly follow the process required by Regulation (EC) 1946/2003 on transboundary movement of genetically modified organisms for its exports of GM mosquito eggs for open release to date, or to obtain informed consent for its experiments (GeneWatch UK, 2012). Oxitec did not send the transboundary notification documents to either the UK or EC authorities in a timely way, with the result that the risk assessments were not publically accessible before the experiments took place: the dates of receipt by the UK authorities are documented in GeneWatch UK (2012); GeneWatch UK received an email from DG SANCO on 28th November 2011 which states: "It seems that at the beginning Oxitec was not well aware of the obligation to copy this information not only to the UK authorities but to the Commission as well (it should not be the UK authorities forwarding this information to the Commission but rather for the exporter to transmit it directly not only to the competent authorities of the country from which the GMO is exported but also to the Commission)". This oversight seems rather surprising given that the company's (ex-Syngenta) head of regulatory affairs has been actively involved in the Cartegena Biosafety Protocol discussions. The risk assessments are of a poor standard and provide inadequate information (GeneWatch UK, 2012; Reeves et al., 2012). The company has not succeeded in publishing its results from its population suppression experiments in the Cayman Islands, despite submitting them to Science in January 2011 (Enserink, 2011): only the results of its small preliminary trial have been published. Oxitec has been strongly criticised for failing to seek informed consent for its releases of GM mosquitoes overseas (Enserink, 2010): it is widely recognised that informed consent is needed for releases of genetically modified disease vectors (Macer, 2003; Macer, 2005). Oxitec's influence on the draft Guidance has clearly been substantive.
692	GeneWatch UK	GBR	Background as provided by the European Commission and	Line 165; It is unclear to the reader why EFSA has produced draft guidance relating to issues so far outside its mandate and expertise, which is to assess and communicate on all risks associated with the food chain. The release of GM insects, fish or mammals (e.g. rabbits) to alter ecosystems through population suppression or altered disease transmission or pollination (bees) may have some impacts on the food chain, but many impacts (such as on disease incidence in humans, or on endangered species or environmentally protected areas) go way beyond this. The Guidance is so

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			EFSA	long and poorly written, with many inconsistencies between sections, that it is difficult to comment fully on it: the number gaps in content (see above comments on Table of Contents), missing references, and framing of the content (particularly problems with applying the concept of toxicological exposure assessment, rather than an ecosystem approach) need to be addressed and a new consultation exercise then needs to be conducted. Although there is useful detail provided on some aspects in some sections, this does not feed through to the document as a whole, and the quality of the GM insects section is particularly poor.
693	GeneWatch UK	GBR	Summary	SUMMARY Line 48: It is unclear to the reader why other animals, e.g. amphibians, molluscs, crustacea, are omitted, despite their inclusion in patent applications (AquaBounty , 2011). The draft Guidance should be clear about whether it is attempting to cover all GM animals or not. Line 57: The summary refers to selection of receiving environments but there is virtually no content in the consultation relating to this or any description of how this might be controlled. For example, the UK company Oxitec is working on genetically modified (GM) Aedes albopictus mosquitoes (Labbé et al. 2012) which are an invasive species currently being monitored due to concerns they will spread tropical diseases in the EU (ECDC, 2009). There is no discussion of whether releases of GM Aedes albopictus would be allowed in parts of the EU but not others and if so, whether they could possibly be restricted to particular receiving environments. There are concerns about how in practice this could be achieved (Angulo & Gilna, 2008a &b). TABLE OF CONTENTS Lines 109-111: A section on Choice of comparators for GM mammals and birds is missing: this should be included. Lines 138 to 144. Specific sections on Pathogens, infections and diseases; Abiotic interactions; and Impact on non-GM animal health and welfare have been omitted from the insects section, despite being included in other sections (fish, mammals and birds). There is no scientific justification for omitting these sections since insects are vectors for many human and animal diseases. In addition, applications such as Oxitec's RIDL (Release of Insects carrying a Dominant Lethal genetic system) insects will result in large numbers of dead GM larvae in the environment, since this is a late-acting lethality system which works mainly at the larval stage (Phuc et al., 2007). There is clearly potential to impact on abiotic processes, as well as on both human and animal health: these sections should therefore be added to the contents. Further, these issues were identified as important in the Expert report to EFSA (Umweltbundesamt, 2010) and their assessment is required by Annex II of Directive 2001/18/EC (EC, 2001).
694	GeneWatch UK	GBR	Abstract	TITLE Line 2, footnote 3. The Working Group on Insects is heavily influenced by the company Oxitec, making EFSA open to allegations of conflicts-of-interest. This does not inspire public confidence. Panel member Michael Bonsall includes his collaboration with Oxitec in his declaration of interests but states incorrectly that Oxford University receives no financial benefit from its relationship with the company: the University is in fact an investor in Oxitec (GeneWatch UK, 2010). Mike Bonsall and Jeff Bale are both members of the UK Advisory Committee on Releases to the Environment (ACRE), where they will presumably both comment on the Guidance they have drafted. It is unclear why Dr Bonsall was required to leave the room when Oxitec's genetically modified diamond back moths were discussed by ACRE (ACRE, 2011) whilst he is allowed to play a central role in drafting EFSA's guidance for the same GM insects. Panel member John Mumford declares his role in the risk assessment project Mosqguide for GM mosquitoes, but does not mention that Oxitec is a partner in this project. Panel member George Christophides declares his role in the FP7 INFRAVEC project, but does not mention that Oxitec is a partner in this project; Romeo Bellini is also a partner in the INFRAVEC project (undeclared). Luke Alphey (an advisor to the panel) declares his role as Chief Scientific Officer at Oxitec and that he has investments in the company and patents on its technology. His declaration notes that Syngenta is funding Oxitec to develop GM Lepidoptera (a large order of insects that includes moths and butterflies). Ex-Syngenta staff who are now working for Oxitec include Oxitec's CEO, Regulatory Affairs Manager and Head of Business Development (http://www.oxitec.com/who-we-are/our-team/). Oxitec's Chair and one of its other Board members are also ex-Syngenta. Oxitec and Syngenta appear to have unduly influenced the draft Guidance, see comments on line 176. ABSTRACT Line 17: It is unclear why other animals e.g. amphibians, molluscs, crustacea are omitted: this means the Guidance is far from comprehensive, even

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				for GM animals envisaged in current patent applications (e.g. AquaBounty, 2011). Due to the extensive errors, omissions and inconsistencies noted in this response (including a need to identify mechanisms through which the many issues which fall outside EFSA's remit can be addressed), there will be a need for re-consultation once revisions have been made. The vast extent of the animal kingdom means that revised guidance should not attempt to encapsulate more than one genus at a time. The scale of the task required to provide meaningful guidance on even a small proportion of possible applications is enormous. For example, there is a current project to sequence the genomes of 5,000 insect and related arthropod species over the next 5 years (i5k: http://arthropodgenomes.org/wiki/i5K). This will create the potential for all these species to be genetically modified in a wide variety of ways.
695	Self	USA	3.8 Aspects of GM animal health and welfare	Chapter 3.8 It"s bad enough that Monsanto has been backed by our government and unleashed onto the world food scene, forcing people to eat FMO food and developing widespread allergies. Isn"t this bad enough ? What gives you the right to mutate animals" genes that would force populations to ultimately ingest these mutated genes ? The human body is not meant to metabolize such food. Keep all animals, pets, and humans safe by not mutating the gene pool and manipulating animals in this way. Besides being completely unethical it is harmful and painful to animals.
696	n/a	GBR	1. Scope of this Guidance Document	165/168 i do not believe the efsa is competent to assess envirolmental risks as it has no remit or expertise in this area
697	Testbiotech	DEU	3.6 Long-term effects	line 1426-1737 The draft Guidance does not give adequate advice on how to address limits of knowledge. While the draft Guidance proposes that uncertainties have to be expressed, the factual limits of knowledge are not integrated within the ERA. Categories of knowledge/ non-knowledge (Boeschen et al., 2006) go beyond the ones of uncertainties. While uncertainty mostly reflects gaps within the strategies and methods being applied for the risk assessment, limits of knowledge can also be used to judge the suitability of the strategies, approaches and methods. Thus, the categories of knowledge /non-knowledge should be addressed on the molecular level as well in regard to the animal and its internal ecology, further on the interactions between the animal with the environment, with biotic and abiotic factors, target and non target organisms, the quality of food etc. This could help to identify the gaps between the risks as described in chapter four and the strategies and methods for risk assessment that are actually available, and give some indication of whether precautionary or preventive measures need to be applied. Another reason why the limits of knowledge should be properly indicated is the necessity of obtaining a better understanding of methods, approaches and strategies that need to be developed in future. In general, identified categories of knowledge and non-knowledge, uncertainties and possible long term effects have to be put in context with the precautionary principle, which is the underlying basis of Directive 2001/18. This most relevant principle is not mentioned in the dossier at all. The high degree of complexity, the factual gaps between potential risks and the available strategies and methods, all go to show that precaution must have priority. Instead of referring to the precautionary principle, EFSA places some emphasis on standard operating procedures (SOPs) that might come into effect if something goes wrong. For example, in line 4360 it is proposed in the context of health risks posed by genetically engineered insects: "when the risk of emerging pathogen(s) is identified, or when in the case of malfunctioning of the GM release technology, implementation of specific standard operative procedures (SOP) to prevent the possible hazard caused by these agents might be required." However, any SPOs applied at a stage when the risks of emerging pathogens are already identified might no longer be effective. Thus, the precautionary principle has to be addressed consistently on all levels of risk assessment and the limits of knowledge have to be identified. References: Boeschen S., ,Kastenhofer, K., Marschall, L., Rust,I., Soentgen, J., Wehling, P., 2006, Scientific Cultures of Non-Knowledge in the Controversy over Genetically Modified Organisms (GMO) The Cases of Molecular Biology and Ecology, GAIA 15/4: 294 – 301

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698	Testbiotech	DEU	2. Strategies for the ERA of GM animals	Line 286-1425 There is major discrepancy between what is described under risks that have to be taken into account during risk assessment (chapter 4) and the specific means and tools as discussed under the strategy of ERA and cross cutting issues. If these discrepancies are not addressed properly, the final Guidance will claim some degree of certainty and safety that is not based on factual scientific evidence. Many of the risks described are multi factorial, nonlinear and emergent therefore they cannot be assessed and predicted by applying the existing strategies for risk assessment. Especially the comparative approach is likely to fail in the light of the risks described in chapter four. Even more than plants, animals have to be considered as heterogenous organisms, they can be described as an ecological system of their own. Animals live in symbiosis with various microorganisms, in addition they can become infected by broad range of viruses, bacteria, parasites and fungi . A further level of complexity is their immune system that is influenced by a broad range of external and internal factors. Animals can move and are exposed to many different environmental conditions that are not limited to sites used for agricultural production. The genetic variation within most animals is higher than within high yield crops used in industrial agriculture. Thus unintended effects can emerge from molecular effects, from specific climatic conditions, special food uptake, infections, changes in the endosymbionds fauna and changes of behaviour. All these factors and their interdependencies can render unintended effects that will hardly be detected by following a comparative approach that was established to investigate only a limited number of criteria under a limited range of conditions. The approach of comparative risk assessment is very much influenced by the DNA centered paradigm of the last century that tries to predict effects in the cell or in organisms and even on the level of ecosystems on the basis of genomic structures. Many of the risks and effects that can be expected in this context are far beyond what can be investigated on the level of the DNA or its products. In the light of recent knowledge about cell biology, including epigenetic, epistatis and pleiotrophic effects (none of them are mentioned in this draft Guidance) and in awareness of many genome x environment interactions, the reductionist model of comparative assessment is no longer adequate. Comparison should be regarded as just a tool, but no longer as a concept. Much more specific strategies and methods such as screening for metabolic and genetic activity have to be applied at an early stage of risk assessment to develop reliable hypotheses for the following steps of risk assessment. A crucial point in the strategy of environmental risk assessment that should be taken into account as a starting point is the question of whether a genetically engineered animal can be controlled in its movements and/ or if it is likely to be persistent or even if it can become invasive. These risks are considered in chapter four, but not enough weight is given to it in the risk assessment strategy. There should be a clear decision making tree within the strategy of environmental risk assessment that integrates this issue. If it is known that a genetically engineered animal cannot be controlled in regard to its persistence and/ or its movements and thus cannot be swiftly be withdrawn if necessary from the environment , prevention has to be applied, the application has to be rejected and no detailed risk assessment performed.

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699	Testbiotech	DEU	1. Scope of this Guidance Document	line 164-285 By taking a look at current risk analysis practice for genetically engineered plants, it is evident that so far risk assessment and important aspects of risk management such as ethics and socio-economic questions are not well harmonised. In general, socio-economic questions and ethics are – if at all – only considered at a late stage in the process of risk analysis. The whole process is mostly driven by the level of risk assessment and does not give sufficient weight to other crucial issues. That is why Testbiotech has already proposed developing an integrated approach of risk analysis for genetically engineered plants in order to bring together the various elements at a much earlier stage in the process (http://www.testbiotech.de/sites/default/files/Testbiotech_Consultation_Commission.pdf). Since animals are – at least from an emotional and ethical point of view – a much more sensitive issue than plants and microorganisms, the overall process of risk analysis cannot be driven by risk assessment. Ethics, socio-economic aspects and participatory decision making involving the perspective of the consumers are issues that will gain much more weight in this context. These aspects should be accepted as the main driving elements during any authorisation process. This will also affect the requirements of risk assessment as, for example, in deciding at which stage animal welfare issues come into play and which criteria have to be applied. The Commission asked EFSA to prepare a Guidance as far back as 2007. The Commission, however, has never managed to identify the essential elements of an overall risk analysis process for genetically engineered animals. In addition, crucial issues relating to the cloning animals for food production still need to be resolved. Based on this observation, EFSA should not adopt any guidance for the environmental risk assessment of genetically engineered animals before the risk manager has done his job, which is to develop an overall framework integrating all aspects of a proper risk analysis. To start by adopting guidance on risk assessment as an isolated element would send the wrong signal to markets and the general public. Such an initiative would not mirror the concerns of civil society groups, consumers, farmers and food producers. In this scenario, EFSA might even be held responsible for failures that are within the remit of the Commission. All in all this draft Guidance touches on highly emotional issues affecting basic interests of consumers, farmers, food producers and general society. At stake are not only basic questions concerning our relationship with mammals and other vertebrates. Civil society should be positioned to be the driving factor in the introduction of new technologies that will so widely affect consumers and food production. EU citizens should not repeatedly be at the mercy of particular economic interests. Besides the debate on ethical and the socio-economical issues, there is another major issue that has to be reiterated when it comes to the scope of this draft Guidance. Many of the aspects discussed here are not related to food production issues, such as the release of genetically engineered insects. As such, these issues are outside of the EFSA mandate and should not be dealt with by the Food Safety Authority, but by another EU body, as for instance, the European Environment Agency (EEA).

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700	Testbiotech	DEU	Assessment	line 164-285 By taking a look at current risk analysis practice for genetically engineered plants, it is evident that so far risk assessment and important aspects of risk management such as ethics and socio-economic questions are not well harmonised. In general, socio-economic questions and ethics are – if at all – only considered at a late stage in the process of risk analysis. The whole process is mostly driven by the level of risk assessment and does not give sufficient weight to other crucial issues. That is why Testbiotech has already proposed developing an integrated approach of risk analysis for genetically engineered plants in order to bring together the various elements at a much earlier stage in the process (http://www.testbiotech.de/sites/default/files/Testbiotech_Consultation_Commission.pdf). Since animals are – at least from an emotional and ethical point of view – a much more sensitive issue than plants and microorganisms, the overall process of risk analysis cannot be driven by risk assessment. Ethics, socio-economic aspects and participatory decision making involving the perspective of the consumers are issues that will gain much more weight in this context. These aspects should be accepted as the main driving elements during any authorisation process. This will also affect the requirements of risk assessment as, for example, in deciding at which stage animal welfare issues come into play and which criteria have to be applied. The Commission asked EFSA to prepare a Guidance as far back as 2007. The Commission, however, has never managed to identify the essential elements of an overall risk analysis process for genetically engineered animals. In addition, crucial issues relating to the cloning animals for food production still need to be resolved. Based on this observation, EFSA should not adopt any guidance for the environmental risk assessment of genetically engineered animals before the risk manager has done his job, which is to develop an overall framework integrating all aspects of a proper risk analysis. To start by adopting guidance on risk assessment as an isolated element would send the wrong signal to markets and the general public. Such an initiative would not mirror the concerns of civil society groups, consumers, farmers and food producers. In this scenario, EFSA might even be held responsible for failures that are within the remit of the Commission. All in all this draft Guidance touches on highly emotional issues affecting basic interests of consumers, farmers, food producers and general society. At stake are not only basic questions concerning our relationship with mammals and other vertebrates. Civil society should be positioned to be the driving factor in the introduction of new technologies that will so widely affect consumers and food production. EU citizens should not repeatedly be at the mercy of particular economic interests. Besides the debate on ethical and the socio-economical issues, there is another major issue that has to be reiterated when it comes to the scope of this draft Guidance. Many of the aspects discussed here are not related to food production issues, such as the release of genetically engineered insects. As such, these issues are outside of the EFSA mandate and should not be dealt with by the Food Safety Authority, but by another EU body, as for instance, the European Environment Agency (EEA).

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701	Testbiotech	DEU	Terms of reference as provided by the European Commission and EFSA	line 164-285 By taking a look at current risk analysis practice for genetically engineered plants, it is evident that so far risk assessment and important aspects of risk management such as ethics and socio-economic questions are not well harmonised. In general, socio-economic questions and ethics are – if at all – only considered at a late stage in the process of risk analysis. The whole process is mostly driven by the level of risk assessment and does not give sufficient weight to other crucial issues. That is why Testbiotech has already proposed developing an integrated approach of risk analysis for genetically engineered plants in order to bring together the various elements at a much earlier stage in the process (http://www.testbiotech.de/sites/default/files/Testbiotech_Consultation_Commission.pdf). Since animals are – at least from an emotional and ethical point of view – a much more sensitive issue than plants and microorganisms, the overall process of risk analysis cannot be driven by risk assessment. Ethics, socio-economic aspects and participatory decision making involving the perspective of the consumers are issues that will gain much more weight in this context. These aspects should be accepted as the main driving elements during any authorisation process. This will also affect the requirements of risk assessment as, for example, in deciding at which stage animal welfare issues come into play and which criteria have to be applied. The Commission asked EFSA to prepare a Guidance as far back as 2007. The Commission, however, has never managed to identify the essential elements of an overall risk analysis process for genetically engineered animals. In addition, crucial issues relating to the cloning animals for food production still need to be resolved. Based on this observation, EFSA should not adopt any guidance for the environmental risk assessment of genetically engineered animals before the risk manager has done his job, which is to develop an overall framework integrating all aspects of a proper risk analysis. To start by adopting guidance on risk assessment as an isolated element would send the wrong signal to markets and the general public. Such an initiative would not mirror the concerns of civil society groups, consumers, farmers and food producers. In this scenario, EFSA might even be held responsible for failures that are within the remit of the Commission. All in all this draft Guidance touches on highly emotional issues affecting basic interests of consumers, farmers, food producers and general society. At stake are not only basic questions concerning our relationship with mammals and other vertebrates. Civil society should be positioned to be the driving factor in the introduction of new technologies that will so widely affect consumers and food production. EU citizens should not repeatedly be at the mercy of particular economic interests. Besides the debate on ethical and the socio-economical issues, there is another major issue that has to be reiterated when it comes to the scope of this draft Guidance. Many of the aspects discussed here are not related to food production issues, such as the release of genetically engineered insects. As such, these issues are outside of the EFSA mandate and should not be dealt with by the Food Safety Authority, but by another EU body, as for instance, the European Environment Agency (EEA).
702	Testbiotech	DEU	Terms of reference as provided by the European Commission and EFSA	line 164-285 Any guidance on risk assessment of genetically engineered animals must be incorporated in an overall framework of risk analysis, integrating aspects of ethics, interests of consumers, the future of agriculture and specific issues of animal welfare. Animals are emotionally sensitive living beings and as such protected by animal welfare regulations. Therefore, introducing genetically engineered animals to the markets cannot be done in the same way as, for example, genetically engineered microorganisms. Opinion polls show that genetic engineering and cloning of animals for food production is a very delicate area that deserves special attention. Many people object to the idea generally of genetically engineering vertebrates to meet economic interests in food production or for fanciful purposes. Genetic engineering interferes with the integrity of the animals on several levels; the integrity of the genome, of the cell, of the individual animal and the overall population. Especially in regard to vertebrates, the ethical debate must not only be about issues of animal welfare, but also take into consideration the integrity of the intrinsic value of animals. To which extent these ethical questions are considered in existing animal welfare

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				legislation has to be discussed in detail before any genetically engineered animals might be allowed to enter the market. It is beyond the mandate of EFSA to deal with these questions. The overall risk analysis has to be performed by the risk manager (the political decision making bodies, especially the EU Commission) thereby integrating ethical and socio-economic issues. However, before the draft Guidance is discussed in further detail, one should first have a look at the overall framework of risk analysis and determine how to integrate the various aspects, and what implications this will have for actual risk assessment.
703	Univ. Perugia	ITA	3.3.2 Choice of comparators for ERA of GM insects	1046 The Guidance recommends a comparator in GM insect replacement strategies as "for GM replacement strategies, which reduce the vector capability of a population without suppressing the population: a wild population in a disease-free location, with any appropriate management scenario (for nuisance impacts, for example);" I am puzzled why a wild population in a disease-free location would be chosen. The reasons a disease is absent is often that the climate or control practices differ from the target replacement area. Therefore, it seems best for the comparator to be an area where climate/ecology/control methods are most similar. The "disease-free" location selection seems both biologically dubious and ethically unnecessary. 2947-8 Not all of these diseases should be capitalized: malaria, dengue fever. Chagas and African should be.
704	Public	GBR	4.1.6 Environmental impacts of the specific techniques used for the management of GM fish	I believe that the all of the proposed is WRONG. Not only for human consumption but for the balance of nature its self. We should NOT mess with nature . We should NOT be told what types of food we are going to have. We should have a choice. If this proposal comes in we will have NO choice! It is our human right to be able to have choice . I protest in the strongest of terms. Please keep me posted.
705	University BOKU	PRT	Background as provided by the European Commission and EFSA	EFSA is not competent to assess environmental risks as it has no remit or expertise in this area.
706	Private Individual	GBR	5. Post-Market Environmental Monitoring plan	I was dismayed to learn that the European Parliament EFSA is running a consultation on a proposal to introduce GM fish, insects, birds, farm animals and pets into the air, land and sea in Britain. The European Food Safety Authority (EFSA) does not have the remit or competence to assess environmental harms should any of these GM animals be released or escape into the British countryside or seas. The consultation ignores the problems there will be keeping a GM-free food supply if these proposals go ahead. There are no plans in the consultation to trace where GM fish or cattle eggs or sperm will end up, or to prevent GM caterpillar eggs from entering the food supply on cabbages or other crops. I will never buy GM food and many people feel the same. However, our freedom to choose will be removed if the environment becomes contaminated with GM. Who gave EFSA the mandate to force GM food onto people who do not want to buy it?

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707	Private Individual	GBR	4. Specific areas of risk to be addressed in the ERA	I was dismayed to learn that the European Parliament EFSA is running a consultation on a proposal to introduce GM fish, insects, birds, farm animals and pets into the air, land and sea in Britain. The European Food Safety Authority (EFSA) does not have the remit or competence to assess environmental harms should any of these GM animals be released or escape into the British countryside or seas. The consultation ignores the problems there will be keeping a GM-free food supply if these proposals go ahead. There are no plans in the consultation to trace where GM fish or cattle eggs or sperm will end up, or to prevent GM caterpillar eggs from entering the food supply on cabbages or other crops. I will never buy GM food and many people feel the same. However, our freedom to choose will be removed if the environment becomes contaminated with GM. Who gave EFSA the mandate to force GM food onto people who do not want to buy it?
708	Private Individual	GBR	3. Cross-cutting considerations	I was dismayed to learn that the European Parliament EFSA is running a consultation on a proposal to introduce GM fish, insects, birds, farm animals and pets into the air, land and sea in Britain. The European Food Safety Authority (EFSA) does not have the remit or competence to assess environmental harms should any of these GM animals be released or escape into the British countryside or seas. The consultation ignores the problems there will be keeping a GM-free food supply if these proposals go ahead. There are no plans in the consultation to trace where GM fish or cattle eggs or sperm will end up, or to prevent GM caterpillar eggs from entering the food supply on cabbages or other crops. I will never buy GM food and many people feel the same. However, our freedom to choose will be removed if the environment becomes contaminated with GM. Who gave EFSA the mandate to force GM food onto people who do not want to buy it?
709	Private Individual	GBR	2. Strategies for the ERA of GM animals	I was dismayed to learn that the European Parliament EFSA is running a consultation on a proposal to introduce GM fish, insects, birds, farm animals and pets into the air, land and sea in Britain. The European Food Safety Authority (EFSA) does not have the remit or competence to assess environmental harms should any of these GM animals be released or escape into the British countryside or seas. The consultation ignores the problems there will be keeping a GM-free food supply if these proposals go ahead. There are no plans in the consultation to trace where GM fish or cattle eggs or sperm will end up, or to prevent GM caterpillar eggs from entering the food supply on cabbages or other crops. I will never buy GM food and many people feel the same. However, our freedom to choose will be removed if the environment becomes contaminated with GM. Who gave EFSA the mandate to force GM food onto people who do not want to buy it?

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710	Private Individual	GBR	1. Scope of this Guidance Document	I was dismayed to learn that the European Parliament EFSA is running a consultation on a proposal to introduce GM fish, insects, birds, farm animals and pets into the air, land and sea in Britain. The European Food Safety Authority (EFSA) does not have the remit or competence to assess environmental harms should any of these GM animals be released or escape into the British countryside or seas. The consultation ignores the problems there will be keeping a GM-free food supply if these proposals go ahead. There are no plans in the consultation to trace where GM fish or cattle eggs or sperm will end up, or to prevent GM caterpillar eggs from entering the food supply on cabbages or other crops. I will never buy GM food and many people feel the same. However, our freedom to choose will be removed if the environment becomes contaminated with GM. Who gave EFSA the mandate to force GM food onto people who do not want to buy it?
711	Private Individual	GBR	Summary	I was dismayed to learn that the European Parliament EFSA is running a consultation on a proposal to introduce GM fish, insects, birds, farm animals and pets into the air, land and sea in Britain. The European Food Safety Authority (EFSA) does not have the remit or competence to assess environmental harms should any of these GM animals be released or escape into the British countryside or seas. The consultation ignores the problems there will be keeping a GM-free food supply if these proposals go ahead. There are no plans in the consultation to trace where GM fish or cattle eggs or sperm will end up, or to prevent GM caterpillar eggs from entering the food supply on cabbages or other crops. I will never buy GM food and many people feel the same. However, our freedom to choose will be removed if the environment becomes contaminated with GM. Who gave EFSA the mandate to force GM food onto people who do not want to buy it?
712	Private Individual	GBR	Terms of reference as provided by the European Commission and EFSA	I was dismayed to learn that the European Parliament EFSA is running a consultation on a proposal to introduce GM fish, insects, birds, farm animals and pets into the air, land and sea in Britain. The European Food Safety Authority (EFSA) does not have the remit or competence to assess environmental harms should any of these GM animals be released or escape into the British countryside or seas. The consultation ignores the problems there will be keeping a GM-free food supply if these proposals go ahead. There are no plans in the consultation to trace where GM fish or cattle eggs or sperm will end up, or to prevent GM caterpillar eggs from entering the food supply on cabbages or other crops. I will never buy GM food and many people feel the same. However, our freedom to choose will be removed if the environment becomes contaminated with GM. Who gave EFSA the mandate to force GM food onto people who do not want to buy it?

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713	N/A	FRA	Abstract	Stop! Stop playing sorcerer"s apprentice! GM vegetal have not shown any proof of benefit for humanity, just income fiancial benefits for their promoters. GM animals have no better fate. Stop! Stop believing you (EFSA experts) have to answer a crooked question : how could GM animals help humanity! This is no question of interest, just short term financial interest in a way to help the new goddess GDP Growth to find something new to destroy. Stop considering poverty as misery : poor people have not ask to give up their culture and to enter into a new world which they do not know the rules. They did not ask for help; don"t set yourself as saviour! Stop taking the starving people of Africa as an excuse : they have no money to buy the solutions promoted by international companies promoting GM animals. Stop cutting this problem into smaller problems, developing a rich vocabulary to describe the technicity of animal properties, as if animals had properties. Simply think to what is behind of this fierce technological research. Simply think about the desaster of BT cotton and the tens of thousands of self-murdereds. Simply think about how Monsanto tried to sell the solution to the desaster Monsanto himself sowed in 2005, into Virginia cotton fields when some giant amaranth grew higher than cooton, blanketing the worthy cotton crop! Monsanto is my friend and Monsanto wants only my money. Monsanto is not alone : several giant companies have the same purpose. EFSA has better research targets that GM-something : protecting biodiversity in the agricultural technics. Just remember mother Nature has already taken thousands of years to answer thousands of real questions: finding the best fit between local weather, local soils and local exposition, local vegetals and local animals. Do not believe someone telling that he may do it better! He"s a liar. And no insurance company will cover the risk the whole humanity may take by allowing him to practice his lies.
714	TiK	GBR	1. Scope of this Guidance Document	1.IS IT WORTH THE RISK? WHAT HAPPENED TO THE PRECAUTIOARY PRINCIPLE? 83% OF PEOPLE IN THE UK DO NOT WANT ANY FORM OF GMO"S, SIMILAR NUMBERS APPLY FOR ALL OF EUROPE, WHERE IS THE DEMOCRACY IN INTRODUCING GMO"S? WHO DOES THIS INITIATIVE BENEFIT? I LOOK FORWARD TO YOUR RESPONSE. VICTORIA BATE

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
715	Agernova	ITA	Background as provided by the European Commission and EFSA	In the world we feed animals ma non nutriamo esseri umani con il cibo per alimentare 3 miliardi di UBA a livello mondiale potremmo sfamare 20 miliardi di Persone Umane. no abbiamo bisogno ne di OGM ne di pesticidi gli ogm si diffondono attraverso il trasferimento genico orizzontale di aprti di DNA modificato, molto reattivo ed è impossibile prevedere cosa succede pertanto non è possibile autorizzare OGM in quanto non rispettano le condizioni di controllo scientifico nel principio di precauzione europeo. Bandire gli OGM è un dovere delle istituzioni Il rispetto della memoria genetica di tutti gli esseri viventi è sancito dalla carta dei diritti dell''Uomo delle Nazioni Unite saluti Prof.Giuseppe Altieri, Agroecologo
716	Agernova	ITA	5.2 General Surveillance (GS)	In the world we feed animals ma non nutriamo esseri umani con il cibo per alimentare 3 miliardi di UBA a livello mondiale potremmo sfamare 20 miliardi di Persone Umane. no abbiamo bisogno ne di OGM ne di pesticidi gli ogm si diffondono attraverso il trasferimento genico orizzontale di aprti di DNA modificato, molto reattivo ed è impossibile prevedere cosa succede pertanto non è possibile autorizzare OGM in quanto non rispettano le condizioni di controllo scientifico nel principio di precauzione europeo. Bandire gli OGM è un dovere delle istituzioni Il rispetto della memoria genetica di tutti gli esseri viventi è sancito dalla carta dei diritti dell''Uomo delle Nazioni Unite saluti Prof.Giuseppe Altieri, Agroecologo
717	Agernova	ITA	Step 4: Risk characterisation	In the world we feed animals ma non nutriamo esseri umani con il cibo per alimentare 3 miliardi di UBA a livello mondiale potremmo sfamare 20 miliardi di Persone Umane. no abbiamo bisogno ne di OGM ne di pesticidi gli ogm si diffondono attraverso il trasferimento genico orizzontale di aprti di DNA modificato, molto reattivo ed è impossibile prevedere cosa succede pertanto non è possibile autorizzare OGM in quanto non rispettano le condizioni di controllo scientifico nel principio di precauzione europeo. Bandire gli OGM è un dovere delle istituzioni Il rispetto della memoria genetica di tutti gli esseri viventi è sancito dalla carta dei diritti dell''Uomo delle Nazioni Unite saluti Prof.Giuseppe Altieri, Agroecologo
718	Agernova	ITA	Abstract	In the world we feed animals ma non nutriamo esseri umani con il cibo per alimentare 3 miliardi di UBA a livello mondiale potremmo sfamare 20 miliardi di Persone Umane. no abbiamo bisogno ne di OGM ne di pesticidi gli ogm si diffondono attraverso il trasferimento genico orizzontale di aprti di DNA modificato, molto reattivo ed è impossibile prevedere cosa succede pertanto non è possibile autorizzare OGM in quanto non rispettano le condizioni di controllo scientifico nel principio di precauzione europeo. Bandire gli OGM è un dovere delle istituzioni Il rispetto della memoria genetica di tutti gli esseri viventi è sancito dalla carta dei diritti dell''Uomo delle Nazioni Unite saluti Prof.Giuseppe Altieri, Agroecologo

	ORGANISATION	COUNTRY	CHAPTER_TEXT	COMMENT_TEXT
719	Individual connected	FRA	2.1.5 Step 5: Risk management strategies	It"s nothing really scientific but only sens. GM animals (and plants) have nothing to do in nature. Nature is ONE and scientific imagination of man it"s just a bit of it. Industrie motivation is not coming out of GOOD principles. To try to prouve we understand the ALL is extrémly prétencious. More we kwow, less we know, as we said since along time ago. There is something out of reach of humain brain, because it is not folowing the sem logical bio-tech patern. Please for ALL, take care .Stop F....
720	association soleil en tête	FRA	Abstract	Je trouve complètement irresponsable de produire des animaux génétiquement modifiés pour la simple raison que même si l"on connait actuellement les différents génomes, les inter actions entre gènes sont parfaitement inconnues la plupart du temps . Aucun scientifique ne peut donc prévoir des conséquences de tels actes. L"humanité a vraiment besoin de recherche et des chercheurs mais dans d"autres domaines .....ne jouons pas avec le feu,... cordialement cyril gravey