REGULATIONS

COMMISSION DELEGATED REGULATION (EU) 2021/525

of 19 October 2020

amending Annexes II and III to Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products ([1]) and in particular Article 85 thereof,

Whereas:

(1) Annexes II and III to Regulation (EU) No 528/2012 set out the information requirements for respectively active substances and biocidal products, which an application for approval of an active substance and an application for authorisation of a biocidal product need to fulfil.

(2) It is necessary to modify the information requirements concerning active substances and biocidal products in order to take into account new methods for generating better information on toxicological properties (such as irritation, neurotoxicity, genotoxicity, etc.), new testing strategies favouring *in vitro* tests over *in vivo* tests in order to reduce testing on vertebrate animals and a testing strategy and methods for the determination of endocrine disrupting properties of substances in accordance with the criteria laid down in Commission Delegated Regulation (EU) 2017/2100 ([2]).

(3) A dossier should be considered as complete if it complies with the requirements of Article 6(1) and Article 20(1), and in particular with the information requirements of Annexes II and III to Regulation (EU) No 528/2012. Pre-submission consultations between the applicant for the approval of an active substance or for the authorisation of a biocidal product and the evaluating competent authority contribute to the quality of the dossier and the progress of the evaluation process. The text of paragraphs 5 and 7, respectively, of points 2 of the introductory parts of Annexes II and III should be modified to ensure that the applicants include the conclusions of such consultation in the application to ensure the smooth operation of the evaluation procedure.

(4) In accordance with Annexes II and III to Regulation (EU) No 528/2012, tests submitted for the purpose of the approval of an active substance or the authorisation of a biocidal product, respectively, are to be conducted in accordance with the methods described in Commission Regulation (EC) No 440/2008 ([3]). As there may be a period between the validation of an internationally recognised test method and its inclusion in Regulation (EC) No 440/2008, point 5 of the introductory parts of Annexes II and III to Regulation (EU) No 528/2012 should be amended to allow applicants to apply the most updated version of test methods.

([1]) OJ L 167, 27.6.2012, p. 1.

([2]) Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council (OJ L 301, 17.11.2017, p. 1).

([3]) Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (OJ L 142, 31.5.2008, p. 1).

(5) Specific rules for the adaptation of the information requirements listed in the first column of the tables in Titles 1 and 2 of Annexes II and III to Regulation (EU) No 528/2012 are limited to concerns related to the recourse to testing on vertebrates. As some requirements listed in that first column do not include testing on vertebrates, the scope of adaptations listed in the third column of the tables listed in Titles 1 and 2 of Annexes II and III should be extended to cover cases where no testing on vertebrates is involved.

(6) Point 2 of Title 1 of Annex II sets out the information requirements for the identification of the active substance. Those requirements need to be adapted in order to allow identification of active substances generated *in situ*.

(7) Point 6 of Title 1 of Annexes II and III set out the requirements for the assessment of the effectiveness of an active substance or a biocidal product, respectively, against target organisms. Such effectiveness should also be demonstrated for the activity of an active substance in the absence of other substances that may affect the effectiveness. For treated articles, the effectiveness of the biocidal properties conferred to the article should be demonstrated. Moreover, the current provisions on unintended side-effects in point 6 do not specify on which type of organisms or objects information should be provided. Therefore, it should be clarified that any observation on undesirable or unintended side effects is to be limited to non-target organisms or objects and material to be protected by the active substance or biocidal product.

(8) Article 62 of Regulation (EU) No 528/2012 requires that testing on vertebrate animals be undertaken only as a last resort. In setting data requirements for the approval of active substances and the authorisation of biocidal products, priority should be given to reliable *in vitro* methods as a substitute to *in vivo* methods requiring the use of vertebrate animals. The testing strategies included in Annexes II and III to Regulation (EU) No 528/2012 therefore need to be adapted to recently validated *in vitro* test guidelines of the Organisation for Economic Cooperation and Development (OECD) and other international standards.

(9) The first mandatory requirement for following up on a positive *in vitro* gene mutation test is currently the *in vivo* unscheduled DNA synthesis (UDS) test, which has inherent limitations and low sensitivity. The Scientific Committee of the European Food Safety Authority ([4]) concluded in an opinion published in November 2017 that negative UDS results are not a proof that a substance does not induce gene mutation. The reference to the UDS test should, therefore, be removed and replaced by a reference to an appropriate *in vivo* somatic cell genotoxicity study.

(10) The current data requirements in Annex II to Regulation (EU) No 528/2012 require a two-generation reproductive toxicity study (TGRTS) to be used to investigate the reproductive toxicity of a substance. That Annex furthermore stipulates that the extended one-generation reproductive toxicity study (EOGRTS) can be considered as an alternative approach to the TGRTS. The EOGRTS offers a number of advantages in comparison to the TGRTS as it assesses in addition to effects on the male and female reproductive system more toxicological effects linked to endocrine-disrupting mode of actions. Therefore, if there is no TGRTS available, an EOGRTS should be performed instead.

(11) Exposure to neurotoxicants *in utero* or during childhood can contribute to a variety of neurodevelopmental and neurological disorders that manifest themselves only as a person ages, and may contribute to neurodegenerative diseases such as Parkinson's or Alzheimer's diseases. To address this concern, test guidelines to adequately screen and characterise active substances potentially toxic for the developing brain should be included in Annex II to Regulation (EU) No 528/2012.

(12) The current structure of the information requirements relating to health data and medical treatment in points 8.12.1 to 8.12.8 of Title 1 of Annex II to Regulation (EU) No 528/2012 may lead to submission of overlapping information under a number of those points. The data requirements should therefore be streamlined to reduce compliance costs and unnecessary delays in the evaluation of applications.

([4]) Scientific Opinion on the clarification of some aspects related to genotoxicity assessment. *EFSA Journal* 2017;15(12):5113, 25 pp. https://doi. org/10.2903/j.efsa.2017.5113

(13) An evaluation of the potential for unintended effects of substances on the immune system should be conducted. However, as no specific developmental immunotoxicity study is available in an OECD test guideline, relevant data should be required to be provided as additional data set.

(14) Point 8.18 of Title 1 of Annex II to Regulation (EU) No 528/2012 duplicates the content of point 13 of that Title and should therefore be deleted.

(15) Point 9.1.1 of Title 1 of Annex II to Regulation (EU) No 528/2012 should be amended in order to clarify when long-term toxicity testing on fish is to be carried out. The list of OECD test methods in point 9.1.6.1 should be replaced in order to take into account on-going developments as regards the information requirements on long-term toxicity studies on fish.

(16) Several information requirements for microorganisms included in Title 2 of Annexes II and III to Regulation (EU) No 528/2012 are either overlapping with other provisions in the Annexes or are irrelevant for microorganisms. Title 2 of Annexes II and III to Regulation (EU) No 528/2012 should therefore be amended in order to eliminate such overlaps and irrelevant information requirements.

(17) The fourth paragraph of point 2 of the introductory part of Annex III to Regulation (EU) No 528/2012 provides that for non-active substances, the applicants are to use the information provided to them in the context of Title IV of Regulation (EC) No 1907/2006 of the European Parliament and of the Council ([5]). That paragraph should be amended in order to clarify that applicants may need to provide additional information on substances of concern included in biocidal products in particular in order to submit a data set that enables the identification of their endocrine disrupting properties.

(18) In order to avoid imposing a disproportionate burden on economic operators, certain tests required by Annex II or Annex III to Regulation (EU) No 528/2012 that were already initiated or carried out before the date of application of this Regulation should be considered appropriate to address the information requirements.

(19) A reasonable period should be allowed to elapse before the data requirements, as modified by this Delegated Regulation become applicable so that the applicants can make the necessary arrangements to meet those requirements. However, in the interests of the protection of human and animal health and of the environment, the applicants should be allowed to apply the changes introduced by this Regulation before its date of application on a voluntary basis.

(20) Regulation (EU) No 528/2012 should therefore be amended accordingly,

HAS ADOPTED THIS REGULATION:

Article 1

Annex II to Regulation (EU) No 528/2012 is amended in accordance with Annex I to this Regulation.

Annex III to Regulation (EU) No 528/2012 is amended in accordance with Annex II to this Regulation.

Article 2

Notwithstanding the date of application of this Regulation laid down in Article 3, applications for approval of an active substance and applications for authorisation of a biocidal product submitted before 15 April 2022 shall be evaluated based on information requirements applicable on the day of submission of such applications.

([5]) Regulation (EC) No 1907/2006 of 18 December 2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), stablishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006, p. 1).

Article 3

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 15 April 2022.

By way of derogation, applicants may choose to apply the data requirements as set out in the Annexes I and II to this Regulation from 15 April 2021.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 19 October 2020.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX I

Annex II to Regulation (EU) No 528/2012 is amended as follows:

(1) the introductory part is amended as follows:

(a) the fifth paragraph of point 2 is replaced by the following:

'The applicant shall initiate a pre-submission consultation with the prospective evaluating body. In addition to the obligation set out in Article 62(2), applicant may also consult with the competent authority that will evaluate the dossier with regard to the proposed information requirements and in particular the testing on vertebrates that the applicant proposes to carry out. The applicant shall document such pre-submission consultations and their outcomes and shall include the relevant documents in the application.';

(b) point 5 is replaced by the following:

'5. Tests submitted for the purpose of the approval of an active substance shall be conducted in accordance with the methods described in Commission Regulation (EC) No 440/2008 (*), or any revised version of these methods not yet included in that Regulation.

However, if a method is inappropriate or not described in Commission Regulation (EC) No 440/2008, other methods shall be used which are scientifically appropriate and their appropriateness shall be justified in the application.

When test methods are applied to nano-materials, an explanation shall be provided of their scientific appropriateness for nanomaterials, and where applicable, of the technical adaptations or adjustments that have been made in order to respond to the specific characteristics of these materials.

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(*) Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (OJ L 142, 31.5.2008, p. 1).';

(2) the table in Title 1 is amended as follows:

(a) the heading of the third column is replaced by the following:

		'Column 3 Specific rules for adaptation from column 1'

(b) row 2 is replaced by the following:

'2	IDENTITY OF THE ACTIVE SUBSTANCE (AND ITS PRECURSOR(S) IF THE ACTIVE SUBSTANCE IS GENERATED *IN SITU*) For the active substance and, if applicable, its precursors, the information given in this Section shall be sufficient to enable the active substance to be identified. If it is not technically possible or if it does not appear scientifically necessary to give information on one or more of the items listed in this Section, the reasons shall be clearly stated'		

(c) row 2.5 is replaced by the following:

'2.5	Molecular and structural formula (including SMILES notation, if available and appropriate). For precursor(s) and for active substances generated *in situ*, information about all generated chemical substances (intended and unintended)		In case it is not possible to exactly define the molecular structure of the precursor(s) and/or active substance, the molecular and structural formulas do not need to be provided'

(d) row 2.8 is replaced by the following:

'2.8	Method of manufacture (syntheses pathways) of active substance including information on starting materials and solvents including suppliers, specifications and commercial availability. For active substances generated *in situ*, a description of the reaction schemes including all intermediate reactions and their associated chemical substances (intended and unintended) shall be provided'		

(e) the following row 2.11.1 is inserted:

'2.11.1	Analytical profile of at least five representative samples taken from the *in situ* generated substance(s), providing information on the content of the active substance(s) and any other constituent above 0,1 % w/w, including residues of precursor(s)'		

(f) row 6.6 is replaced by the following:

'6.6	Efficacy data to support: — the innate activity of the active substance for the intended use(s), and — any claims made on treated articles regarding the biocidal properties conferred to the article. Efficacy data shall include any available standard protocols, laboratory tests or field trials and performance standards where appropriate, or data similar to those available for suitable reference products'		

(g) row 6.7.2 is replaced by the following:

'6.7.2	Observations on undesirable or unintended side effects on non-target organisms or on objects and material to be protected'		

(h) rows 8.1, 8.2 and 8.3 are replaced by the following:

'8.1	Skin corrosion or irritation The assessment shall comprise the following tiers: (a) assessment of the available human, animal and non-animal data; (b) skin corrosion, *in vitro* testing; (c) skin irritation, *in vitro* testing; (d) skin corrosion or irritation, *in vivo* testing		The study/ies in column 1 do(es) not need to be conducted if: — the available information indicates that the substance meets the criteria for classification for skin corrosion or irritation, — the substance is a strong acid (pH≤ 2,0) or base (pH≥ 11,5), — the substance is spontaneously flammable in air or in contact with water or moisture at room temperature, — the substance meets the classification criteria for acute toxicity (Category 1) by the dermal route, or — an acute toxicity study by the dermal route provides conclusive evidence on skin corrosion or irritation adequate for classification. If results from one of the two studies listed in point (b) or point (c) in column 1 of this row already allow conclusive decision on the classification of a substance or on the absence of skin irritation potential, the second study does not need to be conducted An *in vivo* study for skin corrosion or irritation shall be considered only if the *in vitro* studies listed in points (b) and (c) in column 1 of this row are not applicable, or the results of these studies are not adequate for classification and risk assessment

			In vivo studies for skin corrosion or irritation that were carried out or initiated before 15 April 2022 shall be considered appropriate to address this information requirement
8.2	Serious eye damage or eye irritation The assessment shall comprise the following tiers: (a) assessment of the available human, animal and non-animal data; (b) serious eye damage or eye irritation, *in vitro* testing; (c) serious eye damage or eye irritation, *in vivo* testing		The study/ies in column 1 do(es) not need to be conducted if: — the available information indicates that the substance meets the criteria for classification for eye irritation or causing serious damage to eyes, — the substance is a strong acid (pH≤ 2,0) or base (pH≥ 11,5), — the substance is spontaneously flammable in air or in contact with water or moisture at room temperature, or — the substance meets the classification criteria for skin corrosion leading to classification of the substance as "serious eye damage" (category 1). If results from a first *in vitro* study do not allow a conclusive decision on the classification of the substance or on the absence of eye irritation potential (an)other(s) *in vitro* study(ies) for this endpoint shall be considered. An *in vivo* study for serious eye damage or eye irritation shall be considered only if the *in vitro* study(ies) listed in point (b) in column 1 of this row are not applicable, or the results obtained from these studies are not adequate for classification and risk assessment *In vivo* studies for serious eye damage or eye irritation that were carried out or initiated before 15 April 2022 shall be considered appropriate to address this information requirement

‘8.3	Skin sensitisation The information shall allow to conclude whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Category 1A). The information should be sufficient to perform a risk assessment where required The assessment shall comprise the following tiers: (a) assessment of the available human, animal and non-animal data; (b) skin sensitisation, *in vitro* testing. Information from *in vitro* or *in chemico* test method(s) referred to in point 5 of the introductory part of this Annex and addressing each of the following key events of skin sensitisation: (i) molecular interaction with skin proteins; (ii) inflammatory response in keratinocytes; (iii) activation of dendritic cells; (c) skin sensitisation *in vivo* testing. The Murine Local Lymph Node Assay (LLNA) is the first-choice method for *in vivo* testing. Another skin sensitisation test may only be used in exceptional cases. If another skin sensitisation test is used, justification shall be provided		The study/ies in column 1 do(es) not need to be conducted if: — the available information indicates that the substance meets the criteria for classification for skin sensitisation or skin corrosion, — the substance is a strong acid (pH≤ 2,0) or base (pH≥ 11,5), or — the substance is spontaneously flammable in air or in contact with water or moisture at room temperature. *In vitro* tests do not need to be conducted if: — an *in vivo* study referred to in point (c) of column 1 of this row is available, or — the available *in vitro or in chemico* test methods are not applicable for the substance or the results obtained from those studies are not adequate for classification and risk assessment. If information from test method(s) addressing one or two of the key events described under point (b) in column 1 of this row allows for classification of the substance and risk assessment, studies addressing the other key event(s) do not need to be conducted An *in vivo* study for skin sensitisation shall be conducted only if *in vitro* or *in chemico* test methods described under point (b) in column 1 of this row are not applicable, or the results obtained from those studies are not adequate for classification and risk assessment *In vivo* skin sensitisation studies that were carried out or initiated before 15 April 2022 shall be considered appropriate to address this information requirement’

(i) row 8.6 is replaced by the following:

'8.6	*In vivo* genotoxicity study The assessment shall comprise the following tiers: (a) If there is a positive result in any of the *in vitro* genotoxicity studies as listed in 8.5 and there are no reliable results available from an appropriate *in vivo* somatic cell genotoxicity study, an appropriate *in vivo* somatic cell genotoxicity study shall be conducted; (b) A second *in vivo* somatic cell genotoxicity study may be necessary depending on the *in vitro* and *in vivo* results, type of effects, quality and relevance of all available data; (c) If there is a positive result from an *in vivo* somatic cell genotoxicity study available, the potential for germ cell mutagenicity should be considered based on all available data, including toxicokinetic evidence to demonstrate whether the substance has the capacity to reach germ cells. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered	ADS	The study/ies in column 1 do(es) not need to be conducted if: — the results are negative for the three *in vitro* tests listed in 8.5 and no other concern has been identified (e.g. metabolites of concern formed in mammals), or — the substance meets the criteria to be classified as a germ cell mutagen category 1A or 1B. The germ cell genotoxicity test does not need to be conducted if the substance meets the criteria to be classified as a carcinogen, category 1A or 1B and a germ cell mutagen category 2'

(j) rows 8.10 to 8.10.3 are replaced by the following:

'8.10	Reproductive toxicity For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route		The studies do not need to be conducted if: — the substance meets the criteria to be classified as a genotoxic carcinogen (classified both as germ cell mutagen category 2, 1A or 1B and carcinogenic category 1A or 1B), and appropriate risk management measures are implemented including measures related to reproductive toxicity, — the substance meets the criteria to be classified as a germ cell mutagen category 1A or 1B and appropriate risk management measures

		are implemented including measures related to reproductive toxicity, — the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available provided that the dataset is sufficiently comprehensive and informative), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma or blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and the pattern of use indicates that there is no or negligible human or animal exposure, — the substance meets the criteria to be classified as reproductive toxicity category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment, then no further testing for sexual function and fertility will be necessary. A full justification must be provided and documented if investigations for developmental toxicity are not conducted, or — the substance is known to cause developmental toxicity, meeting the criteria for classification as reproductive toxicity category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. A full justification must be provided and documented if investigations for sexual function and fertility is not conducted.

			Notwithstanding the provisions of this column of this row, studies on reproductive toxicity may need to be conducted to obtain information on endocrine disrupting properties as laid down in 8.13.3.1.
8.10.1	Pre-natal development toxicity study (OECD TG 414) on two species, preferred first species is rabbit (non-rodent) and preferred second species is rat (rodent); oral route of administration is the preferred route		The study on the second species shall not be conducted if the study performed on the first species or other available data indicate that the substance causes developmental toxicity meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment
8.10.2	Extended One-Generation Reproductive Toxicity Study (OECD TG 443), with cohorts 1A and 1B and extension of cohort 1B to include the F2 generation with the aim to produce 20 litters per dose group, F2 pups must be followed to weaning and investigated similarly as F1 pups. Rat is the preferred species and oral route of administration is the preferred route. The highest dose level should be based on toxicity and selected with the aim to induce reproductive and/or other systemic toxicity		A two-generation reproductive toxicity study conducted in accordance with OECD TG 416 (adopted 2001 or later) or equivalent information shall be considered appropriate to address this information requirement, if the study is available and was initiated before 15 April 2022.
8.10.3	Developmental neurotoxicity Developmental Neurotoxicity Study in accordance with OECD TG 426, or any relevant study (set) providing equivalent information, or cohorts 2A and 2B of an Extended One-Generation Reproductive Toxicity study (OECD TG 443) with additional investigation for cognitive functions		The study shall not be conducted if the available data: — indicate that the substance causes developmental toxicity and meets the criteria to be classified as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and — are adequate to support a robust risk assessment'

(k) the following row 8.10.4 is inserted:

'8.10.4	Further studies A decision on the need to perform additional studies including those informing on the mechanisms should be based on the outcomes of the studies listed in 8.10.1, 8.10.2 and 8.10.3 and all other relevant available data	ADS'	

(l) row 8.11.2 is replaced by the following:

'8.11.2	Carcinogenicity testing in a second species (a) A second carcinogenicity study should be conducted using the mouse as test species; (b) For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route		The second carcinogenicity study does not need to be conducted if the applicant can justify on the basis of scientific grounds that it is not necessary'

(m) rows 8.12.1 to 8.12.8 are replaced by the following:

'8.12.1	Information on signs of poisoning, clinical tests, first aid measures, antidotes, medical treatment and prognosis following poisoning		
8.12.2	Epidemiological studies		
8.12.3	Medical surveillance data, health records and case reports'		

(n) rows 8.13.2 and 8.13.3 are replaced by the following:

'8.13.2	Neurotoxicity If the active substance is an organophosphorus compound or if there is an indication, knowledge of the mechanism of action or knowledge from acute or repeated dose studies that the active substance may have neurotoxic properties, additional information or specific studies (such as OECD TG 424 or OECD TG 418 or 419 or equivalent) will be required If anticholinesterase activity is detected a test for response to reactivating agents should be considered	ADS	

	For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route		
8.13.3	Endocrine disruption The assessment of endocrine disruption shall comprise the following tiers: (a) An assessment of the available information from the following studies and any other relevant information, including *in vitro* and *in silico* methods: (i) 8.9.1 A 28-day oral toxicity study in rodents (OECD TG 407); (ii) 8.9.2 A 90-day oral toxicity study in rodents (OECD TG 408); (iii) 8.9.4 A repeated dose oral toxicity study in non-rodents (OECD TG 409); (iv) 8.10.1 A prenatal developmental toxicity study (OECD TG 414); (v) 8.10.2 An extended one-generation reproductive toxicity study (OECD TG 443) or two-generation reproductive toxicity study (OECD TG 416); (vi) 8.10.3 A developmental neurotoxicity study (OECD TG 426); (vii) 8.11.1 A combined carcinogenicity study and long-term repeated dose toxicity study (OECD TG 451-3); (viii) A systematic review of the literature including studies on mammals and non-mammalian organisms; (b) If there is any information suggesting that the active substance may have endocrine disrupting properties, or if there is incomplete information on key parameters relevant		Where sufficient weight of evidence to conclude on the presence or absence of a particular endocrine disrupting mode of action is available: — further testing on vertebrate animals for that effect shall be omitted for that mode of action, — further testing not involving vertebrate animals may be omitted for that mode of action. In all cases, adequate and reliable documentation shall be provided'

	for concluding on endocrine disruption, then additional information or specific studies shall be required to elucidate: (1) the mode or the mechanism of action; and/or (2) potentially relevant adverse effects in humans or animals For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to consider the oral route and conduct animal studies by the oral route		

(o) the following row 8.13.3.1 is inserted:

'8.13.3.1	Specific additional studies to investigate potential endocrine disrupting properties may include, but are not limited to the following: (a) the mammalian toxicity studies listed in 8.13.3(a); (b) the *in vitro* assays: (i) Estrogen receptor transactivation assay (OECD TG 455); (ii) Androgen receptor transactivation assay, (OECD TG 458); (iii) H295R steroidogenesis assay (OECD TG 456); (iv) the Aromatase assay (human recombinant) OPPTS 890.1200; (c) Uterotrophic bioassay in rodents (OECD TG 440) and Hershberger bioassay in rats (OECD TG 441); (d) Pubertal development and Thyroid Function in Intact Juvenile or Peripubertal Male Rats (OPPTS 890.1500). The decision to carry out studies in mammals shall be taken based on all available information, including a systematic review of the literature (including information on endocrine disrupting effects in non-target organisms) and the availability of suitable *in silico or in vitro* methods	ADS'	

(p) rows 8.13.4 and 8.13.5 are replaced by the following:

'8.13.4	Immunotoxicity and developmental immunotoxicity If there is any evidence from repeat dose or reproductive toxicity studies that the active substance may have immunotoxic properties, then additional information or specific studies shall be required to elucidate: (1) the mode or the mechanism of action; and/or (2) potentially relevant adverse effects in humans or animals. For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to consider the oral route and conduct animal studies by the oral route	ADS	

8.13.5	Further mechanistic studies A decision on the need to perform additional studies should be based on all relevant data	ADS'	

(q) row 8.18 is deleted;

(r) row 9.1.1 is replaced by the following:

'9.1.1	Short-term toxicity testing on fish When short-term fish toxicity data is required, the threshold approach (tiered strategy) should be applied. A long-term toxicity testing on fish in accordance with point 9.1.6.1 shall be considered if the substance is poorly water soluble, i.e. below 1 mg/L		The study does not need to be conducted if: — a valid long-term aquatic toxicity study on fish is available, — sufficient weight of evidence including the use of other data such as the Fish Embryo Acute Toxicity (FET, OECD TG 236) and/or results obtained from non-animal methods is available for this data requirement'

(s) row 9.1.6.1 is replaced by the following:

'9.1.6.1	Long term toxicity testing on fish The information shall be provided from long-term toxicity testing on fish in which early life-stages (eggs, larvae or juveniles) are exposed	ADS'	

(t) row 9.10 is replaced by the following:

‘9.10	Endocrine disruption The assessment of endocrine disruption properties shall comprise the following tiers: (a) An assessment of the mammalian data set in accordance with 8.13.3 to assess whether the substance has endocrine disrupting properties based on data in relation to mammals; (b) If it cannot be concluded based on the mammalian data in accordance with 8.13.3 or 9.1.6.1 that the substance has endocrine disrupting properties, then studies set out in 9.10.1 or 9.10.2 shall be considered taking account of any other available relevant information, including a systematic review of the literature’		

(u) the following rows 9.10.1, 9.10.2 and 9.10.3 are inserted:

‘9.10.1	Endocrine disruption in fish Specific studies to investigate potential endocrine disrupting properties may include, but are not limited to the following data requirements: (a) Medaka extended one-generation test (MEOGRT, OECD TG 240); (b) Fish life cycle toxicity test (FLCTT, OPPTS 850.1500) covering all the ‘estrogen-, androgen- and steroidogenic-mediated’ (EAS) parameters foreseen to be measured in the MEOGRT study		The study does not need to be carried out if: — there is no indication for endocrine activity or endocrine related effects from a sufficient mammalian data set in accordance with 8.13.3 or from any other relevant information (e.g. literature), and — valid *in vivo* data is available, with no information suggesting that the active substance may elicit endocrine activity or effects potentially related to endocrine activity in either the Fish short term reproduction assay (FSTRA; OECD TG 229), or the 21-days fish assay (OECD TG 230) or Fish sexual developmental test (FSDT, OECD TG 234). If other data are available covering the estrogenic, androgenic and steroidogenic, (EAS) related

			modalities or parameters investigated in OECD TG 229 or OECD TG 230 or OECD TG 234, then those data can be used instead
9.10.2	Endocrine disruption in amphibians Specific additional studies to investigate potential endocrine disrupting properties may include, but are not limited to Larval amphibian growth and development assay (LAGDA; OECD TG 241)		The study does not need to be carried out if: — there is no indication for endocrine activity or endocrine related effects from a sufficient mammalian data set in accordance with 8.13.3 or from any other relevant information (e.g. literature), and — valid *in vivo* data is available, with no information suggesting that the active substance may have endocrine disrupting properties in an Amphibian metamorphosis assay (AMA; OECD 231)
9.10.3	If there is information suggesting that the active substance may have endocrine disrupting properties, or if there is incomplete information on key parameters relevant for concluding on endocrine disruption, additional information or specific studies, as necessary, shall be required to elucidate: (a) the mode or the mechanism of action; and/or (b) potentially relevant adverse effects in humans or animals.	ADS'	

(3) the table in Title 2 is amended as follows:

(a) the heading of the third column is replaced by the following:

		'Column 3 Specific rules for adaptation from column 1'

(b) row 2.4 is replaced by the following:

'2.4	Specification of the technical grade active ingredient'		

(c) the following rows 2.4.1, 2.4.2 and 2.4.3 are inserted:

'2.4.1	Content of the active micro-organism and identity and content of relevant metabolites or toxins		
2.4.2	Identity and content of impurities, additives, contaminating micro-organisms		
2.4.3	Analytical profile of batches'		

(d) row 2.5 is replaced by the following:

'2.5	Method of production and quality control'		

(e) rows 2.6 to 2.9 are deleted;

(f) row 3.5 is replaced by the following:

'3.5	Information on the production of relevant metabolites and toxins'		

(g) rows 4.1 and 4.2 are replaced by the following:

'4.1	Methods, procedures and criteria used to establish the presence and identity of the micro-organism		
4.2	Analytical methods for the analysis of the micro-organism as manufactured'		

(h) the following row 4.3 is inserted:

'4.3	Methods used for monitoring purposes to determine and quantify residues (viable or non-viable)'		

ANNEX II

Annex III to Regulation (EU) No 528/2012 is amended as follows:

(1) the introductory part is amended as follows:

(a) the fourth paragraph of point 2 is replaced by the following:

'For some of the information requirements set out in this Annex, it may be possible to satisfy these requirements based on available information of the properties of the active substance(s) contained in the product and the properties of non-active substance(s) included in the product. For non-active substances, applicants shall use the information provided to them in the context of Title IV of Regulation (EC) No 1907/2006, where relevant, and the information made available by the Agency in accordance with point (e) of Article 77(2) of that Regulation. However, the information may be not sufficient or adequate to determine whether a non-active substance contained in a biocidal product has hazardous properties and the evaluating body may conclude that further data are required.';

(b) the seventh paragraph of point 2 is replaced by the following:

'The applicant shall initiate a pre-submission consultation with the prospective evaluating body. In addition to the obligation set out in Article 62(2), the applicant may also consult with the competent authority that will evaluate the dossier with regard to the proposed information requirements and in particular the testing on vertebrates that the applicant proposes to carry out. The applicant shall document such pre-submission consultations and their outcomes and shall include the relevant documents in the application.';

(c) point 5 is replaced by the following:

'5. Tests submitted for the purpose of authorisation shall be conducted in accordance with the methods described in Commission Regulation (EC) No 440/2008, or any revised version of these methods not yet included in that Regulation.

However, if a method is inappropriate or not described in Commission Regulation (EC) No 440/2008, (*) other methods shall be used which are scientifically appropriate and their appropriateness shall be justified in the application.

When test methods are applied to nano-materials, an explanation shall be provided of their scientific appropriateness for nanomaterials, and where applicable, of the technical adaptations or adjustments that have been made in order to respond to the specific characteristics of these materials.

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(*) Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (OJ L 142, 31.5.2008, p. 1).';

(2) the table in Title 1 is amended as follows:

(a) the heading of the third column is replaced by the following:

		'Column 3 Specific rules for adaptation from column 1'

(b) row 6.6 is replaced by the following:

'6.6	The proposed claims for the product and, where claims are made, for treated articles regarding the biocidal properties conferred to the article'		

(c) row 6.8.2 is replaced by the following:

'6.8.2	Observations on undesirable or unintended side-effects on non-target organisms or on objects and material to be protected'		

(d) Rows 8.1, 8.2 and 8.3 are replaced by the following:

'8.1	Skin corrosion or irritation The assessment shall comprise the following tiers: (a) assessment of the available human, animal and non-animal data; (b) skin corrosion, *in vitro* testing; (c) skin irritation, *in vitro* testing; (d) skin corrosion or irritation, *in vivo* testing		Testing of the product or mixture does not need to be conducted if: — there are sufficient valid data on each component of the product or mixture to allow its classification in accordance with Regulation (EC) No 1272/2008, and synergistic effects between any of the components are not expected, — the product or mixture is a strong acid (pH≤ 2,0) or base (pH≥ 11,5), — the product or mixture is spontaneously flammable in air or in contact with water or moisture at room temperature, — the product or mixture meets the classification criteria for acute toxicity category 1 by the dermal route, or — an acute toxicity study by the dermal route provides conclusive evidence on skin corrosion or irritation adequate for classification. If results from one of the two studies listed in points (b) or (c) in column 1 of this row already allow conclusive decision on the classification of product or mixture or on the absence of skin irritation potential, the second study does not need to be conducted An *in vivo* study for skin corrosion or irritation shall be considered only if the *in vitro* studies listed in points (b) and (c) in column 1 of this row are not applicable, or the results of these studies are not adequate for classification and risk assessment and the calculation method or

			bridging principles laid down in Regulation (EC) No 1272/2008 are not applicable *In vivo* studies for skin corrosion or irritation that were carried out or initiated before 15 April 2022 shall be considered appropriate to address this information requirement
8.2	Serious eye damage or eye irritation The assessment shall comprise the following tiers: (a) assessment of the available human, animal and non-animal data; (b) serious eye damage or eye irritation, *in vitro* testing; (c) serious eye damage or eye irritation, *in vivo* testing		Testing on the product or mixture does not need to be conducted if: — there are sufficient valid data available on each component of the product or mixture to allow its classification in accordance with Regulation (EC) No 1272/2008, and synergistic effects between any of the components are not expected, — the product or mixture is a strong acid (pH≤ 2,0) or base (pH≥ 11,5), — the product or mixture is spontaneously flammable in air or in contact with water or moisture at room temperature, or — the product or mixture meets the classification criteria for skin corrosion leading to its classification as "serious eye damage" category 1 If results from a first *in vitro* study do not allow a conclusive decision on the classification of the product or mixture or on the absence of eye irritation potential (an)other(s) *in vitro* study(ies) for this endpoint shall be considered An *in vivo* study for serious eye damage or eye irritation shall be considered only if the *in vitro* study(ies) under point (b) in column 1 of this row are not applicable, or the results obtained from these studies are not adequate for classification and risk assessment and

			the calculation method or bridging principles laid down in Regulation (EC) No 1272/2008 are not applicable *In vivo* studies for serious eye damage or eye irritation that were carried out or initiated before 15 April 2022 shall be considered appropriate to address this information requirement
8.3	Skin sensitisation The information shall allow to conclude whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Category 1A). The information should be sufficient to perform a risk assessment where required The assessment shall comprise the following tiers: (a) assessment of the available human, animal and non-animal data; (b) skin sensitisation, *in vitro* testing. Information from *in vitro* or *in chemico* test method(s) conducted in accordance with point 5 of the introductory part of this Annex and addressing each of the following key events of skin sensitisation: (i) molecular interaction with skin proteins; (ii) inflammatory response in keratinocytes; (iii) activation of dendritic cells. (c) skin sensitisation *in vivo* testing. The Murine Local Lymph Node Assay (LLNA) is the first-choice method for *in vivo* testing. Another skin sensitisation test may only be used in exceptional circumstances. If another skin sensitisation test is used, scientific justification shall be provided.		Testing on the product or mixture does not need to be conducted if: — there are sufficient valid data available on each component of the product or mixture to allow its classification in accordance with Regulation (EC) No 1272/2008, and synergistic effects between any of the components are not expected, — the available information indicates that the product or mixture should be classified for skin sensitisation or skin corrosion, — the product or mixture is a strong acid (pH≤ 2,0) or base (pH≥ 11,5), or — the product or mixture is spontaneously flammable in air or in contact with water or moisture at room temperature. *In vitro* tests do not need to be conducted if: — an *in vivo* study referred to in point (c) in column 1 of this row is available, or — the available *in vitro or in chemico* test methods are not applicable for the product or mixture or the results obtained from these studies are not adequate for classification and risk assessment. If information from test method(s) addressing one or two of the key events described in point (b) in column 1 of this row already allows

		for classification of the substance and risk assessment, studies addressing the other key event(s) do not need to be conducted An *in vivo* study for skin sensitisation shall be considered only if *in vitro* or *in chemico* studies referred to in point (b) in column 1 of this row are not applicable, or the results obtained from these studies are not adequate for classification and risk assessment and the calculation method or bridging principles laid down in Regulation (EC) No 1272/2008 are not applicable *In vivo* studies for skin sensitisation that were carried out or initiated before 15 April 2022 shall be considered appropriate to address this information requirement'

(e) row 8.7 is replaced by the following:

'8.7	Available toxicological data relating to: (a) non-active substance(s) (i.e. substance(s) of concern); and (b) a mixture that a substance(s) of concern is a component of Tests listed in Section 8 of the table in Title 1 of Annex II shall be carried out for the substance(s) of concern or a mixture that a substance(s) of concern is a component of if insufficient data are available and cannot be inferred through read-across, *in silico* or other accepted non-testing approaches		Testing on the product or mixture does not need to be conducted if all of the following conditions are met: — there are valid data available on each of the components in the mixture to allow classification of the mixture in accordance with the rules laid down in Regulation (EC) No 1272/2008, — a conclusion can be made whether the biocidal product can be considered as having endocrine disrupting properties, — synergistic effects between any of the components are not expected'

(f) row 9.1 is replaced by the following:

'9.1	Available ecotoxicological data relating to: (a) non-active substance(s) (i.e. substance(s) of concern); (b) a mixture that a substance(s) of concern is a component of		Testing on the product or mixture does not need to be conducted if all the following conditions are met: — there are valid data available on each of the components in the mixture to allow classification of

Tests listed in Section 9 of Title 1 of Annex II shall be carried out for the substance(s) of concern or a mixture that a substance(s) of concern is a component of if insufficient data are available and cannot be inferred through read-across, *in silico* or other accepted non-testing approaches		the mixture in accordance with the rules laid down in Regulation (EC) No 1272/2008, — a conclusion can be made whether the biocidal product can be considered as having endocrine disrupting properties, — synergistic effects between any of the components are not expected.'

(3) the table in Title 2 is amended as follows:

(a) the heading of the third column is replaced by the following:

		'Column 3 Specific rules for adaptation from column 1'

(b) row 2.3 is replaced by the following:

'2.3	Detailed quantitative (g/kg, g/l, % w/w (v/v), cfu/g, cfu/l or IU/mg or any other appropriate unit) and qualitative information on the constitution, composition and function of the biocidal product, e.g. micro-organism, active substance(s) and non-active substances and any other relevant components All relevant information on individual ingredients and the final composition of the biocidal product shall be given'		

(c) rows 3.6.8 to 3.6.12 are deleted

(d) the following rows 3.6.8 and 3.6.9 are inserted:

'3.6.8	Spraying patterns – aerosols		

3.6.9	Other technical characteristics'		

(e) rows 4 to 4.12.3 are replaced by the following

4. PHYSICAL HAZARDS AND RESPECTIVE CHARACTERISITICS		
'4.1. Explosives		
4.2. Flammable aerosols		

4.3. Flammable liquids		
4.4. Flammable solids		
4.5. Oxidising liquids		
4.6. Oxidising solids		
4.7. Corrosive to metals		
4.8. Other physical indications of hazard		
4.8.1. Auto-ignition temperatures of products (liquids and gases)		
4.8.2. Relative self-ignition temperature for solids		
4.8.3. Dust explosion hazard'		

(f) row 10.3 is replaced by the following:

'10.3 Leaching behaviour and/or mobility	ADS'	