CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion on the peer review of the pesticide risk assessment of the active substance diphenylamine[1]

European Food Safety Authority[2]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Diphenylamine is one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002[3] as amended by Commission Regulation (EC) No 1095/2007.[4] This Regulation requires the European Food Safety Authority (EFSA) upon request of the European Commission to organise a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by the designated rapporteur Member State and to provide within 6 months a conclusion on the risk assessment to the European Commission.

Ireland being the designated rapporteur Member State submitted the DAR on diphenylamine in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 20 June 2007. The peer review was initiated on 8 October 2007 by dispatching the DAR for consultation of the Member States and the applicants Cerexagri s.a. and Pace International. Subsequently, the comments received on the DAR were examined and responded by the rapporteur Member State in the reporting table. This table was evaluated by EFSA to identify the remaining issues. The identified issues as well as further information made available by the applicant upon request were evaluated in a series of scientific meetings with Member State experts in May - June 2008.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in September 2008 leading to the conclusions set out in the EFSA Conclusion issued on 30 September 2008 in the EFSA Scientific Report (2008) 188.

Following the Commission Decision of 30 November 2009 (2009/859/EC)[5] concerning the non-inclusion of diphenylamine in Annex I to Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant, the European Diphenylamine Task Force made a resubmission application for the inclusion of diphenylamine in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008. The resubmission dossier included further data in response to the issues identified in the conclusions leading to the Decision on non-inclusion, as set out in the Review Report (SANCO/191/08) as follows:

> The information available is insufficient to satisfy the requirements set out in Annex II and Annex III Directive 91/414/EEC in particular with regard to:
>
> - the risk to consumers.

[1] On request from the European Commission, Question No EFSA-Q-2011-00232, approved on 2 December 2011.
[2] Correspondence: pesticides.peerreview@efsa.europa.eu
[3] OJ No L 224, 21.08.2002, p. 25, as amended by Regulation (EC) No 1095/2007 (OJ L 246, 21.9.2007, p. 19)
[4] OJ L 246, 21.9.2007, p. 19
[5] OJ L 314, 1.12.2009, p. 79

Suggested citation: European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance diphenylamine. EFSA Journal 2012;10(1):2486. [59 pp.]. doi:10.2903/j.efsa.2012.2486. Available online: www.efsa.europa/efsajournal.htm

And concerns were identified with regard to

- the lack of data on the levels and toxicity of unidentified metabolites of the substance;
- the possible formation of nitrosamines during storage of the active substance and during processing of treated apples;
- the lack of data on the potential breakdown or reaction product of diphenylamine residues in processed commodities;
- the lack of data to finalise the specification.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, Ireland, being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report. The Additional Report was received by the EFSA on 3 December 2010.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States on 13 December 2010 and the applicant on 11 January 2011, for comments. The EFSA collated and forwarded all comments received to the European Commission on 24 February 2011.

In accordance with Article 20, following consideration of the Additional Report and the comments received, the European Commission requested the EFSA to deliver its conclusions on diphenylamine.

The conclusion from the original review was reached on the basis of the evaluation of the representative use as a plant growth regulator as proposed by the applicant. It is applied as a post-harvest drench to apples before they go into storage. The conclusion of the peer review of the resubmission was reached on the basis of the evaluation of the same representative use. Full details of the representative use can be found in Appendix A.

The representative formulated product for the evaluation was "No Scald DPA 31", an emulsifiable concentrate (EC).

Adequate methods are available to monitor all compounds given in the respective residue definition, except for surface water and products of animal origin. Residues in food of plant origin can be determined with a multi-method (the German S19 method has been validated). For the other matrices only single methods are available to determine residues of diphenylamine. A data gap is identified for a method of analysis for products of animal origin and for surface water.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

In the mammalian metabolism studies, diphenylamine was rapidly and completely absorbed after oral administration, it underwent extensive metabolism to sulphonyl and glucuronyl conjugates and was rapidly excreted mainly via urine. Acute oral and dermal toxicity were low; it was not technically feasible to perform an acute toxicity study by inhalation. Diphenylamine was not a skin irritant, but can cause severe irritation to the eyes; therefore, classification with **Xi "irritant"** and risk phrase **R41 "risk of serious damage to eyes"** was proposed. According to a Magnusson and Kligman test, diphenylamine was not a skin sensitizer.

The red blood system was the target organ of diphenylamine in rats, mice and dogs, upon short-term and long-term exposure, as evidenced by altered haematological parameters, splenic erythropoiesis, splenic congestion and haemosiderosis. Additionally, histopathological changes in the liver and kidneys were found upon longer exposure. The relevant short-term NOAEL of 9.6 - 10 mg/kg bw/day

was derived from the 90-day rat, 90-day dog and 1-year dog studies. The relevant long-term NOAEL was the dose level of 7.5 mg/kg bw/day from the 2-year rat study.

No genotoxic potential was attributed to diphenylamine; no carcinogenicity was observed in either rats or mice. Reproductive effects were limited to reduced implantation sites in F_1 females associated with reduced litter size at clear parental toxic doses (reduced food intake/body weight gain and haemolytic condition). No effect on development was attributed to diphenylamine administration in rat or rabbit.

No neurotoxic alert was evident in the data package provided.

The Acceptable Daily Intake (ADI) of diphenylamine was 0.075 mg/kg bw/day based on the 2-year rat study, applying a safety factor of 100; the Acceptable Operator Exposure Level (AOEL) was 0.1 mg/kg bw/day based on the 90-day rat, 90-day and 1-year dog studies, and applying a safety factor of 100; no Acute Reference Dose (ARfD) was allocated. As no study was provided, default dermal absorption value of 100% was assumed for risk assessment. The level of operator exposure calculated for the representative formulation "No Scald DPA 31" was below the AOEL according to the mixing and loading phase of the German model when operators wear gloves. Considering the very specific indoor use of diphenylamine, bystander and re-entry worker exposure were not considered relevant. The worker exposure (interpreted as sorting out and packaging fruits activities) risk assessment relates to the automated handling of the treated fruits; manual handling of the fruits has not been taken into consideration.

The metabolism of diphenylamine was investigated in apples at different time intervals after a post-harvest treatment by dipping. Over the course of the study a penetration of the radiolabelled residues was observed from the surface of the fruit into the pulp. Upon analysis diphenylamine was always the major residue, however identification of metabolites was considered insufficient by the meeting of experts and therefore a data gap was set to address the identity of the metabolites coded 1, 2 and 3 detected in significant amounts in the apple samples. Also the potential for presence or formation of nitrosamines in apple metabolism or during processing is not excluded and has to be investigated according to a fully validated analytical method. This data gap is linked to the data gap set to address the nature of the residues in the apple processed commodities. The residue definition for monitoring was set as diphenylamine alone whilst the residue definition for risk assessment could only provisionally be proposed as the parent compound, pending the outcome of the additional data to address the identity of the metabolites 1, 2 and 3 and also the potential presence of nitrosamines both in apple extracts and in processed commodities.

Livestock metabolism and feeding studies in ruminants were evaluated and considered as acceptable. The applicant made a case that treated apples are destined only for direct human consumption and will not be part of livestock diet. However, since any restriction with respect to the use of treated apples or commodities derived from treated apples in animal feeding is not in the remit of the risk assessor, a "worst case" assessment has to be carried out assuming livestock exposure to diphenylamine residues from treated apples in order to derive MRLs for animal matrices. The residue definition for monitoring was set as diphenlyamine alone, while for risk assessment EFSA proposed to include both diphenylamine and the conjugates of 4-hydroxy diphenylamine since these metabolites were found to be predominant in milk. The residue definition for risk assessment has to be regarded as provisional pending the outcome of the additional data on the nature and magnitude of the residues in apple wet and dry pomace and the recalculation of the livestock dietary burden.

The consumer risk assessment is not finalised due to the identified data gaps on the identity and toxicological profile of metabolites coded 1, 2, and 3 in raw apples, the nature of the breakdown products under processing conditions, the potential occurrence of nitrosamines in raw and processed apples and the storage stability of diphenylamine residues in the residue trials samples.

The only data available in the dossier that were pertinent to the fate and behaviour of diphenylamine in the environment were the results that it exhibits moderate water solubility, is stable to sterile aqueous hydrolysis, exhibits very low persistence in direct aqueous photolysis experiments in the laboratory

(optimised light conditions) and is moderately volatile. Indirect photooxidation in the atmosphere through reaction with hydroxyl radicals was also estimated. However it was concluded that despite these limited data, as a consequence of the applied for intended use of diphenylamine, this information was sufficient to characterise the environmental risk at the EU level as exposure of soil, surface water and sediment and consequently groundwater would be expected to be negligible. Though diphenylamine is moderately volatile, significant concentrations in air would not be expected as this property will be counteracted by its moderate water solubility. Diphenylamine would not be expected to have the potential for long range atmospheric transport due to its expected potential for indirect photochemical oxidative degradation in the atmosphere.

The submitted data suggest a low acute and short-term toxicity of diphenylamine to birds and a low acute toxicity to mammals. Exposure of birds and mammals from the representative use as an indoor drench treatment of apples is considered unlikely. Diphenylamine is very toxic to aquatic organisms. However exposure of aquatic organisms is considered to be negligible. Management measures tailored to local practice and legislation should be put in place to control the waste disposal of spent application solution and prevent accidental spillage entering sewers or surface water drains.

No data were made available for other non-target organisms. However exposure of non-target organisms is assumed to be unlikely if the product is applied according to the GAP and studies are considered not necessary. The risk to biological methods of sewage treatment was assessed as low.

KEY WORDS

diphenylamine, peer review, risk assessment, pesticide, plant growth regulator

TABLE OF CONTENTS

BACKGROUND

Legislative framework

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000 as amended by Commission Regulation (EC) No 1095/2007, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State (RMS). Diphenylamine is one of the 84 substances of the third stage, part B, covered by the Regulation (EC) No 1490/2002 designating Ireland as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, Ireland submitted the report of its initial evaluation of the dossier on diphenylamine, hereafter referred to as the draft assessment report (Ireland, 2007), received by EFSA on 20 June 2007. Following an administrative evaluation, the draft assessment report was distributed for consultation in accordance with Article 11(2) of the Regulation (EC) No 1095/2007 on 8 October 2007 to the Member States and the applicants Cerexagri s.a. and Pace International as identified by the rapporteur Member State.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, EFSA identified and agreed on lacking information to be addressed by the applicant as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the applicant, a scientific discussion took place in expert meetings in May – June 2008. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in September 2008 leading to the conclusions set out in the EFSA Conclusion issued on 30 September 2008 in the EFSA Scientific Report 188 (EFSA, 2008a).

Following the Council Decision of 30 November 2009 (2009/859/EC)[6] concerning the non-inclusion of diphenylamine in Annex I to Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant the European Diphenylamine Task Force made a resubmission application for the inclusion of diphenylamine in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008.[7] The resubmission dossier included further data in response to the issues identified in the conclusions leading to the Decision on non-inclusion, as set out in the Review Report (SANCO/191/08; European Commission, 2009b) as follows:

> The information available is insufficient to satisfy the requirements set out in Annex II and Annex III Directive 91/414/EEC in particular with regard to:
>
> - the risk to consumers.
>
> And concerns were identified with regard to
>
> - the lack of data on the levels and toxicity of unidentified metabolites of the substance;
> - the possible formation of nitrosamines during storage of the active substance and during processing of treated apples;

[6] OJ L 314, 1.12.2009, p. 79
[7] OJ L 15, 18.01.2008, p. 5

- the lack of data on the potential breakdown or reaction product of diphenylamine residues in processed commodities;
- the lack of data to finalise the specification.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, Ireland, being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report (Ireland, 2010). The Additional Report was received by the EFSA on 3 December 2010.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States on 13 December 2010 and to the applicant on 11 January 2011, for comments. The EFSA collated and forwarded all comments received to the European Commission on 24 February 2011. The collated comments were also forwarded to the RMS for compilation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 2 of the Reporting Table. The comments and the applicant's response were evaluated by the RMS in column 3.

In accordance with Article 20, following consideration of the Additional Report and the comments received, the European Commission decided to further consult the EFSA. By written request, received by the EFSA on 25 March 2011, the European Commission requested the EFSA to arrange a consultation with Member State experts as appropriate and deliver its conclusions on diphenylamine within 6 months of the date of receipt of the request, subject to an extension of a maximum of 90 days where further information were required to be submitted by the applicant in accordance with Article 20(2).

The scope of the peer review and the necessity for additional information, not concerning new studies, to be submitted by the applicant in accordance with Article 20(2), was considered in a telephone conference between the EFSA, the RMS, and the European Commission on 25 March 2011; the applicant was also invited to give its view on the need for additional information. On the basis of the comments received, the applicant's response to the comments, and the RMS' subsequent evaluation thereof, it was concluded that there was no need for EFSA to organise a consultation with Member State experts, and that further information should be requested from the applicant in the area of physical and chemical properties.

The outcome of the telephone conference, together with EFSA's further consideration of the comments is reflected in the conclusions set out in column 4 of the Reporting Table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table were reported in the final column of the Evaluation Table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in October 2011.

The conclusion from the original review was reached on the basis of the evaluation of the representative use as presented in the DAR, i.e. use as plant growth regulator by acting as an anti-oxidant against the physiological disorder scald in apples. The conclusion of the peer review of the resubmission was reached on the basis of the evaluation of the same representative use. A list of the relevant end points for the active substance as well as the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the Peer Review Report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The Peer Review Report (EFSA, 2011) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the comments received,
- the Reporting Table (28 March 2011),
- the Evaluation Table (23 November 2011),
- the comments received on the draft EFSA conclusion.

Given the importance of the Additional Report including its addendum (compiled version of July 2011 containing all individually submitted addenda; Ireland, 2011) and the Peer Review Report, both documents are considered respectively as background documents A and B to this conclusion. The documents of the Peer Review Report (EFSA, 2008b) and the final addendum (Ireland, 2008) developed and prepared during the course of the initial review process are made publicly available as part of the background documentation to the original conclusion, issued on 30 September 2008 (EFSA, 2008a).

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Diphenylamine is the IUPAC name of this compound. It has no ISO common name.

Diphenylamine is used as a plant growth regulator. It does this by acting as an anti-oxidant against the physiological disorder scald. There continues to be much debate about the cause of storage scald in apples, but most agree that storage scald is a type of chilling injury. The general theory is that alpha-farnesene, a naturally occurring volatile terpene in the apple fruit, is oxidized to a variety of products (conjugated trienes). These oxidation products result in injury to the cell membranes which eventually result in cell death in the outermost cell layers of the fruit. The representative formulated product for the evaluation was "No Scald DPA 31", an emulsifiable concentrate (EC).

The evaluated representative use is as a post-harvest drench treatment for apples. Full details of the GAP can be found in the list of endpoints.

CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion: SANCO/3030/99 rev.4 (European Commission, 2000) and SANCO/825/00 rev. 7 (European Commission, 2004a).

The minimum purity of diphenylamine as manufactured is 987 g/kg. However, a full specification of the starting material is missing.

The technical material contains aniline, 4-aminobiphenyl and 2-aminobiphenyl which are relevant impurities. The maximum content in the technical material should not be higher than 5 mg/kg aniline, 2 mg/kg 4-aminobiphenyl and 6.5 mg/kg 2-aminobiphenyl.

There was a second source mentioned in the DAR, PACE International which wanted to demonstrate equivalence. However, insufficient data were available to conclude on equivalence and this source was not considered further.

The content of diphenylamine in the representative formulation is 318 g/L (pure). It is likely that when product containers are opened diphenylamine is degraded and therefore appropriate labelling should be considered.

The main data regarding the identity of diphenylamine and its physical and chemical properties are given in Appendix A.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of diphenylamine in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material and the relevant impurities in the formulation. Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are available to monitor all compounds given in the respective residue definitions except for surface water, i.e. diphenylamine in food of plant origin; and diphenylamine in soil, water and air. A method is not available for the D3[8] isomers in surface water. A method is not available for products of animal origin and, as MRLs will be set, a data gap has been identified.

Residues in apples are analysed using the German S19 method, this is published with a LOQ of 0.05 mg/kg. Water, soil and air are analysed by LC-MS/MS methods, the LOQ for soil is 0.01 mg/kg, 0.02

[8] D3: 3,4-dihydrocyclopenta[*b*]indol-7-ol and 1,4-dihydrocyclopenta[*b*]indol-7-ol

µg/L for ground and drinking water and 0.05 µg/L for surface water. The LOQ for air was 0.0025 mg/m^3. A method is available for the analysis of human plasma with a LOQ of 0.05 mg/l the data gap for the method for products of animal origin will cover the need for a method for tissues.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/222/2000 rev. 7 (European Commission, 2004b), SANCO/10597/2003 – rev. 8.1, May 2009 (European Commission, 2009a).

Diphenylamine was discussed at the PRAPeR Expert's Meeting on mammalian toxicology (PRAPeR 49) in June 2008, no expert consultation was required upon resubmission.

The PRAPeR 49 meeting agreed that there are three relevant impurities based on their toxicological profile and their classification for health effects: aniline, 4-aminobiphenyl and 2-aminobiphenyl, whose level should stay at a minimum. At the maximum concentration proposed by the applicant in the volume 4 of the Draft Assessment Report (Ireland, 2007), no concern is raised.

The batches used in the toxicological studies are considered to be representative of the technical specification as presented in the Additional Report (Ireland, 2010).

2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

Diphenylamine was rapidly and completely absorbed after oral dosing, based on total recovery in urine, cage wash and tissues/carcass. Distribution appeared to be limited considering the low residue levels found in tissues, although pharmacokinetic determinations were limited. Diphenylamine was almost completely metabolised to more polar compounds through oxidative hydroxylation of the phenyl ring moieties and production of aryl-*O*-sulphonyl conjugates and *O*- and *N*-glucuronyl conjugates. Only 1 - 3 % of the dose was recovered as parent in faeces, no parent was found in urine. Elimination was rapid; the majority of the administered dose was excreted through urine and faeces within 24 to 48 hours, the main route being through urine.

2.2. Acute toxicity

Oral and dermal acute toxicity of diphenylamine were low. It was noted that contradictory information exists referring to old/published oral studies with limited information; studies confirming the existing classification with T, R23/24/25 and R33 were not available. The experts agreed that the study presented in the draft assessment report was more reliable to base the oral LD_{50} (as higher than 15 g/kg bw) for diphenylamine. The applicant demonstrated that it was not technically feasible to perform an acute toxicity study by inhalation. Diphenylamine was not irritating to skin; in the rabbit eye irritation study, 1 out of 6 animals showed severe and persisting eye effects, the experts proposed to classify the active substance as **Xi "irritant"**, and risk phrase **R41 "risk of serious damage to eyes"** based on this finding, and on the weight of evidence from other published studies. No potential for skin sensitisation was found in a Magnusson and Kligman test in guinea pigs.

2.3. Short-term toxicity

The oral short-term effects of diphenylamine were investigated in four 90-day studies in rat, mouse and dog and a 1-year study in dog by dietary administration; a 21-day dermal study in rabbit was also presented.

The red blood system was the target organ in all three species, and there was evidence in the rat and the dog of interference with normal liver function.

In mouse the NOAEL was the dose level of 1.7 mg/kg bw/day, based on altered red blood cell parameters, splenic erythropoiesis, splenic congestion and haemosiderosis at 94 mg/kg bw/day.

The NOAEL in rat was the dose level of 9.6 mg/kg bw/day, based on altered red blood cell parameters, compensatory haematopoiesis in spleen, marrow and liver, splenic congestion and haemosiderosis at 96 mg/kg bw/day.

In dogs, the dose level of 10 mg/kg bw/day elicited increased serum cholesterol in one (of the two) 90-day study and increased total bilirubin in the 1-year study. The experts agreed that, without any other associated findings, these effects should not be considered as adverse and **the overall NOAEL in dogs was set at this dose of 10 mg/kg bw/day**. Higher doses of diphenylamine caused clinical signs such as diarrhoea, mucus, discoloured faeces and urine, pale skin and emesis, marked non-regenerative anaemia, changes in liver, kidney, gallbladder, thyroid and spleen weights.

Dermal application of diphenylamine did not produce overt indications of toxicity in rabbits up to 1000 mg/kg bw/day; however, due to the presence of gross stomach lesions at the dose level of 500 mg/kg bw/day and up, the NOAEL was the low dose level of 100 mg/kg bw/day.

2.4. Genotoxicity

Diphenylamine was tested in three *in vitro* and two *in vivo* assays measuring different endpoints of potential genotoxicity such as gene mutation and chromosomal aberration.

Results from mutagenicity studies indicated that diphenylamine does not induce base pair substitution or frame-shift mutation in any of the bacterial strains tested. The gene mutation test in mouse lymphoma cells revealed a marginal positive effect in the presence of metabolic activation. In this assay, the effect was associated with some toxicity and the increases in mutant frequency observed were relatively small. In the chromosomal aberration test with Chinese hamster ovary cells, weak clastogenic effects were observed in the presence of an exogenous metabolic activation at concentrations toxic to the cells.

No mutagenic effect was observed in the *in vivo* micronucleus test in mice or in the *in vivo/in vitro* unscheduled DNA synthesis (UDS) assay in rat hepatocytes.

The weight of evidence suggests weak effects of diphenylamine on chromosomes in the presence of metabolic activation *in vitro*. However, based on the unequivocal, negative results in the two *in vivo* studies and the equivocal nature of *in vitro* results, no genotoxic potential is attributed to diphenylamine.

2.5. Long-term toxicity

Long-term toxicity of diphenylamine was examined in a two-year study in rat and an 18-month study in mouse.

In rats, the main target was the haematopoietic system, mainly the erythrocytes; signs of toxicity included reduced body weight, increased spleen and liver weights, splenic congestion with haemosiderosis and histopathological changes in the spleen, kidney and liver. **The NOAEL was the dose level of 7.5 mg/kg bw/day.**

Increased mortality was observed in mice treated with 368.0 mg/kg bw/day and up, mainly due to cystitis in males and amyloidosis in females. Increased breakdown and elimination of erythrocytes was observed upon long-term administration of diphenylamine with compensatory haematopoiesis causing congestion and haemosiderosis of the spleen, pyelonephritis and cystitis with dilation of the urinary bladder in males and amyloidosis in females. The LOAEL was the dose level of 73.2 mg/kg bw/day.

No indication of carcinogenicity was found in either rats or mice.

2.6. Reproductive toxicity

Reproductive toxicity of diphenylamine was tested in a two-generation reproduction toxicity study in rat and a developmental toxicity study in rat and in rabbit, each preceded by a range finding study.

Reproduction toxicity

Main parental effects in the two-generation study were consistent with effects observed in short-term studies indicative of haemolytic condition, beginning from the lower dose of 32 mg/kg bw/day with liver and spleen histopathology. Reduced food intake and body weight gain, and increased liver, spleen and kidney weights were observed from the dose of 92 mg/kg bw/day on, associated with reduced pup weights in the F_2 generation.

All reproductive parameters were comparable to controls with the exception of reduced implantation sites in the F_1 females at the highest dose of 327 mg/kg bw/day, and therefore reduced litter size in this generation. The parental systemic NOAEL was below 32 mg/kg bw/day, the offspring's NOAEL was the low dose of 32 mg/kg bw/day and the reproductive NOAEL was 92 mg/kg bw/day.

Developmental toxicity

In the developmental toxicity study in rat, the maternal NOAEL was 50 mg/kg bw/day based on reduced body weight gain and increased spleen weight associated with histopathological changes at 100 mg/kg bw/day. No developmental effect was observed up to the highest dose tested; therefore the developmental NOAEL was 100 mg/kg bw/day.

In rabbit, signs of maternal toxicity at the top dose consisted of a moderate initial weight loss, which was not completely reversed at the end of the study, and reduced food intake. The maternal NOAEL was the dose level of 100 mg/kg bw/day. The developmental NOAEL was the highest dose tested of 300 mg/kg bw/day as no adverse effect was observed on the development of foetuses.

2.7. Neurotoxicity

No study was provided. Diphenylamine does not belong to a chemical group known to induce neurotoxicity, no concern was raised from the other general studies, and therefore no study was required.

2.8. Further studies

No study was submitted. Pending on the identification of metabolites in the residues, toxicological information on these metabolites may be required; pending on consumer exposure to nitrosamines coming from the residues a toxicological assessment might be needed to set limits of exposure or reference values for these compounds of toxicological concern (refer to data gaps in section 8). Regarding the metabolites 4-hydroxy diphenylamine and the glucuronic acid conjugate of 4-hydroxy diphenylamine, their toxicological profile is covered by the toxicological assessment conducted with the parent.

2.9. Medical data

Annual health surveillance carried out on workers potentially exposed to diphenylamine did not indicate any specific adverse effect on the health of employees.

2.10. Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD)

ADI

Initially in the draft assessment report (Ireland, 2007), the rapporteur Member State proposed an ADI of 0.03 mg/kg bw/day based on the 1-year dog study considering a LOAEL of 10 mg/kg bw/day, and a higher safety factor of 300 due to the uncertainties related to the absence of a NOAEL.

The experts changed the LOAEL of the dog study to a NOAEL during the PRAPeR 49 meeting, and considered the long-term rat study as appropriate to derive the ADI. The **ADI for diphenylamine was established at 0.075 mg/kg bw/day** based on the NOAEL of 7.5 mg/kg bw/day from the 2-year rat study and a standard safety factor of 100.

AOEL

The same approach as referred above was proposed initially by the rapporteur Member State to derive an AOEL of 0.03 mg/kg bw/day, based on the LOAEL from the 1-year dog study and a higher safety factor (300).

The experts agreed to base the AOEL on the 90-day rat study with a NOAEL of 9.6 mg/kg bw/day; 90-day and 1-year dog studies each with a NOAEL of 10 mg/kg bw/day and applying a safety factor of 100. Since oral absorption was quite complete, no correction factor is required relative to oral absorption. **The resulting AOEL was 0.1 mg/kg bw/day.**

ARfD

Diphenylamine was of low acute toxicity and revealed no effect of concern with respect to an acute intake. **No ARfD was allocated.**

2.11. Dermal absorption

No data was submitted. The molecule is small and has a high lipophilic potential. A 100 % default dermal absorption value is required according to the guidance document on dermal absorption (European Commission, 2004b).

2.12. Exposure to operators, workers and bystanders

The representative plant protection product "No Scald DPA 31" is an emulsifiable concentrate (EC) formulation containing 318 g diphenylamine/L.

Diphenylamine is used post-harvest in indoor drench tanks on apples to control storage scald (as an antioxidant) prior to entering storage.

Operator exposure

Estimation of operator exposure was recalculated in the post PRAPeR experts Meeting addendum to Volume 3 of July 2008 (Ireland, 2008) based on the parameters agreed at the PRAPeR expert meeting.

Two application methods were described: drive through drencher and automated bin drencher; it was concluded that the mixing and loading elements of the German model were appropriate to assess the operator exposure as the operator is not exposed to spray in either of the two application methods proposed. A maximum volume of treatment solution of 2000 L/day was assumed to represent the European scenarios with a maximum concentration of diphenylamine of 2 g/L in the treatment solution and an operator body weight of 60 kg.

According to this model, estimated operator exposure was below the AOEL only when gloves were worn.

Estimated operator exposure presented as % of AOEL (0.1 mg/kg bw/day)

German model	No PPE	With PPE (a)
Mixing and loading operations	160	1.6

(a) PPE (personal protective equipment): gloves

It is noted that the assessment of operator exposure derived from collateral activities to drenching operations was not presented in the DAR (Ireland, 2007) or in the Additional Report (Ireland, 2010). Considering the available risk assessment where operators are estimated to be exposed to 1.6% of the AOEL for diphenylamine when gloves are worn (derived from mixing and loading activities only), and the specific type of application requiring compliance with good industrial hygiene, it is unlikely that the threshold value would be exceeded for the remaining potential exposure of operators.

Worker exposure

Considering the very specific process of application of diphenylamine in enclosed indoor areas, and the fact that fruits are stored until sale, no additional procedures involving re-entry workers are necessary. The worker exposure (interpreted as sorting out and packaging fruits activities) risk assessment relates to the automated handling of the treated fruits; manual handling of the fruits has not been taken into consideration.

Bystander exposure

According to the specific uses of diphenylamine, the presence of bystanders is not allowed during treatments; therefore bystander exposure was not considered relevant.

3. Residues

The conclusions in the residue section below are based on the guidance documents listed in the document 1607/VI/97 rev.2 (European Commission, 1999).

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

The metabolism was investigated in apples, after dipping of the fruits in a treatment solution containing ^{14}C-diphenylamine labelled on the phenyl ring at a dose rate equivalent to 2800 g a.s./hl (14 N rate). Upon application the apples were kept in cold storage at *ca.* 0°C and samples were taken for analysis on the day of application and at intervals of 12, 24 and 40 weeks after application.

The amount of total radioactive residues found in the whole apple remained relatively constant within 24 weeks after treatment (50 - 55 mg/kg), but decreased to 37 mg/kg after 40 weeks. Over the course of the study a penetration of the radioactive residues was observed from the surface of the fruit into the pulp. Hence the residue level in the pulp steadily increased within 40 weeks from 1% TRR (0.6 mg/kg) to 27% TRR (10 mg/kg) while residues on the apple surface and in the peel declined correspondingly from 99% TRR (54 mg/kg) to 73% TRR (27 mg/kg) over the storage period.

Upon analysis of the surface wash, peel and pulp tissue diphenylamine was the main residue present at all sampling time points. Up to 2 weeks diphenylamine was the only component identified. A consistent decline to 54% of TRR (20 mg/kg) was observed after 40 weeks of storage. LC-MS analysis identified the following metabolites: the hydroquinone of diphenylamine up to 4.9% TRR, 1.8 mg/kg), the O-glucose ester conjugate of diphenylamine (up to 7% TRR, 3.3 mg/kg), and a mixture of

hydroxydiphenylamine and the quinone of hydroxy-diphenylamine (up to 7.9% TRR, 2.9 mg/kg), present at the 12, 24 and 40 weeks interval. In addition three unidentified metabolite fractions coded 1, 2 and 3 were characterised in the samples at 40 weeks, but not identified. The unknown compounds coded 1, 2 and 3 contributed to a relevant part of the total residues at 40 weeks storage interval (16.3 % TRR - 6.1 mg/kg). Compound 3 was also found in samples taken at 12 weeks interval. These three unknown metabolite fractions are expected to be present individually at a level greater than 0.05 mg/kg when apples are treated at N rate. Therefore, the meeting of experts agreed to define a data gap to address the identity of the metabolites 1, 2 and 3 detected in significant amounts in treated apples.

In response to the case provided by the applicant that the unknown metabolites were not detected at 24 weeks, and that this interval would be representative for the storage time for apples in the EU market, the experts noted that analysis at the selected sampling time points between 0 and 40 weeks is considered to provide a snapshot rather than a continuous picture of the presence of metabolites over time. For instance, unknown component 3 was present in samples at 12 weeks (2.1 mg/kg) while not found at 24 weeks, but was again detected at 40 weeks (0.96 mg/kg).Whether or not the three unknown compounds could be present at any time point other than the chosen sampling time points is not known from the available data. Moreover, the meeting was not able to conclude on a maximum storage period for apples from treatment until consumption, and therewith to definitely exclude longer storage periods than 24 weeks, considering transport and distribution on the market, stockage by retailers and eventually storage by consumers subsequent to the release of stored diphenylamine treated apples from the warehouses.

Given the structure of diphenylamine and indications of the possible formation of nitrosamines in the case of incorrect tank mixing (see report of PRAPeR Expert Meeting 46 in EFSA, 2008b), the applicant was asked to address whether there could be a probability of formation of nitrosamines in metabolism or under processing. The meeting could not exclude the natural presence of nitrosating agents (nitrites/nitrates) in apples but did not know the significant level at which the formation of nitrosamines could be induced. In the Additional Report to the DAR, samples of the apple extracts from the initial metabolism study were analysed for the determination of potential nitrosamines by 2D-TLC analysis using a visualisation agent for the detection of nitrosamine functional groups. EFSA is of the opinion that, based on the outcome of the tentative identification of the nitrosamines by this analytical method, there is no clear evidence that metabolites containing the nitrosamine function are not present in the apple extracts since this type of analytical method might show insufficient resolution and a lack of selectivity. Moreover, the method was not validated according to the current requirements at a determined LOQ. Therefore, the data gap remains for the applicant to investigate the potential presence of nitrosamines in the treated apple extracts according to a fully validated analytical method. This data gap is linked to the data gaps regarding further clarification of identity of the metabolites 1, 2 and 3 in raw apples and the nature of the residues in apple processed commodities.

The residue definition for monitoring purposes is set as diphenylamine alone as it was the predominant compound of the total residues in apple extracts throughout all storage time intervals. The proposed residue definition as parent compound for risk assessment will need to be revised pending the submission of data addressing the identity of the unknown metabolites 1, 2 and 3 in raw apples, the breakdown and reaction products in processed apple matrices according to the standard hydrolytic conditions, the potential presence of nitrosamines and also the toxicological properties of these unknown compounds. The proposed residue definitions are restricted to the use as a post-harvest drench treatment on fruits.

A total of five residue trials carried out in France (2002) and USA (1994) were submitted to support the notified representative use. In the studies the terminal diphenylamine residues in fresh and stored apples following post-harvest drench application of diphenylamine at the maximum notified use rate were quantified. The treated apples were stored in controlled atmosphere for a maximum period of 260 days (37 weeks) and samples were taken for analysis at different intervals following application (90, 120, 180, 210 days).

The results in the decline study from France (3 trials) confirmed the observation made in the metabolism study with respect to residue levels remaining relatively constant for up to 180 days (25 weeks) after treatment. The highest residue value in one of these trials was found at the 180 days sampling interval. In one trial of the US studies diphenylamine levels were found to decline slowly but constantly over the storage period of 260 days while in the second trial residues in the whole apple were only determined at day 0 after the drench application.

From the total of trials the critical residue values for diphenylamine in apple ranged between 1.19 and 3.37 mg/kg. After extensive discussion on whether or not the available data showed the level of homogeneity expected for post-harvest treated crops, as set out in the guidance document,[9] the majority of experts eventually decided not to require additional residue trial data for the drench application.

It should be noted that residue trials with dip application were also submitted and reported in the DAR, but this mode of application is no longer supported by the applicant. These residue trials showed higher residues than in trials with drench application, but their assessment has been considered as out of the remit of the peer review.

If it is concluded that besides the parent compound the residue definition for risk assessment should include additional metabolites, further residue trials might be necessary to analyse the level of these compounds in order to perform a reliable consumer dietary risk assessment.

Submitted data on freezer storage stability indicated that the residues of diphenylamine can be considered as stable for up to 5 months in whole apples and pomace, and for up to 7 months in apple juice. No storage stability data were provided to cover the maximum storage period of the samples (260 days) in the residue trials. A data gap was therefore identified during the resubmission to provide additional storage stability data to cover the storage period of the samples from the residue trials.

In the initial DAR, no study was provided to investigate the nature of the potential breakdown or reaction products of diphenylamine residues in processed commodities. The applicant made a case that apples destined for commercial processing will typically not be treated with diphenylamine, and therefore submission of such data was not relevant. However, the case made does not consider the possibility of treated apples being purchased by consumers and used in household preparations (cooked apple, apple purée etc...). This case has to be considered, and therefore the experts agreed that investigations as set out in the guidance document[10] should be performed. A new data gap to submit data on the nature of the residues in apple processed commodities has been identified. In the frame of the resubmission (Additional Report to the DAR, November 2010), a new study was provided to investigate the nature of the residues in processed commodities from apples that were treated with ^{14}C-diphenylamine and stored for 12 and 36 weeks. The apples stored for 12 and 36 weeks, respectively were juiced, blended, chopped and then cooked at 180 °C for 30 minutes prior to sample extraction. The applicant considered that these conditions were representative of household processing conditions and covered pasteurisation and sterilisation. In addition, characterization of the extracts of the processed apple samples confirmed the presence of the parent diphenylamine but the identification of the other recovered metabolites, amongst them the potential unknown metabolites 1, 2 and 3, was inconclusive. EFSA concluded that the processing study is not representative of the standard hydrolytic conditions and therefore the data gap still remains to address the nature of the residues in processed apples according to the representative processing conditions of pasteurisation (apple juice), baking/cooking and sterilisation (cooked/baked apples, purée). This data gap is also linked to the data gap on the determination of the potential presence of nitrosamines.

In the DAR, a study on the level of residues in processed apple commodities was submitted. Levels of parent diphenylamine were determined in the raw apple and in the processed commodities. Processing

[9] Guidance document SANCO 7525/VI/95 rev. 9: Guidelines on comparability, extrapolation, group tolerances and data requirements (European Commission, 2011).
[10] Guidance document SANCO/7035/VI/95 rev.5 on processing studies (European Commission, 1999).

factors for apple juice and wet and dry apple pomace could be derived. Diphenylamine did not concentrate in juice processed from treated apples while the residue levels in pomace exceeded the levels initially found in the whole fruit. The meeting of experts noted inconsistency in the residue levels recovered in wet and dry pomace. Usually levels of diphenylamine are expected to be higher in dry pomace than in wet pomace due to concentration by loss of water, unless a degradation of diphenylamine occurred during the drying process. A data gap was identified regarding further clarification of the results from the processing studies, i.e. to confirm the residue levels determined for wet and dry pomace. In the addendum provided after the PRAPeR 50 experts' meeting (July 2008), the applicant confirmed that the supplied information regarding the residue levels of diphenylamine respectively in wet and dry pomace was correct. Both the applicant and the rapporteur Member State also assumed that since diphenylamine is considered as moderately volatile, some loss would be expected during the drying process. EFSA considers that a degradation of diphenylamine cannot be excluded and a data gap to confirm the magnitude of the residues in apple wet and dry pomace is pending the outcome of the additional data to address the nature of the residues in apple processed commodities.

3.1.2. Succeeding and rotational crops

Since the representative use is a post-harvest treatment during storage, studies on residues in rotational and succeeding crops are not a requirement to support the notified use in apples.

3.2. Nature and magnitude of residues in livestock

Metabolism studies were carried out with lactating goats and laying hens. Diphenylamine is considered as a fat-soluble compound and is therefore expected to accumulate in the tissues.

Only pomace is used as a feed item in the diet of the ruminants. Since apple pomace is not fed to laying hens, MRLs are not required for poultry tissues and eggs. The applicant considered that diphenylamine has not to be applied on apples destined for industrial processing into apple juice, and consequently apple pomace should not contain any diphenylamine residues. Only apples destined for direct human consumption are usually treated with diphenylamine, and these apples are not intended for consumption by livestock. In that specific case, a livestock exposure assessment is not triggered. The experts basically agreed. However, a question mark was raised by the experts over the fate of treated apples that could not be marketed until the following year's harvest. The RMS was asked for further clarification regarding the feed practices in all the Member States and therefore on the need to perform a quantitative livestock exposure assessment. In the Additional Report to the DAR, a few Member States (UK, Germany, Ireland, the Netherlands) confirmed that the leftover apples were not fed to animals and that they were either sent to landfill, used for the production of biogas, used as a fertiliser or exported outside the European area. It is noted that any restriction with respect to the use of treated apples, or commodities derived from treated apples, in animal feeding is not in the remit of the risk assessor. For the moment, as a precautionary measure, the experts agreed that a 'worst case' assessment should be carried out by assuming livestock exposure to diphenylamine residues from treated apples, in order to forecast if under these conditions MRLs would have to be proposed. To decide if this evaluation will be relevant for the representative use, risk managers should consider whether or not livestock exposure can indeed be excluded. The experts considered the available livestock metabolism studies as valid and acceptable. The rapporteur Member State also confirmed that the feeding dose rates in the goat metabolism study were expressed as "as received" and EFSA recalculated the average feeding dose rate as 1.86 mg/kg bw/d.

In the goat metabolism study diphenylamine was identified as the major residue in kidney and omental fat (36% TRR), and was also present at a lower level in milk (12% TRR) and liver (6% TRR). In addition, respectively in milk, kidney and liver, up to 86%, 38% and 11% of the total residues were identified as the glucuronic acid and sulfate conjugates of the 4-hydroxy diphenylamine. These conjugates were not recovered in fat. The total radioactive residues in muscle were too low (<0.01 mg/kg) to attempt any further characterization of the residues.

For monitoring purposes the residue definition for food of animal origin is proposed as diphenylamine alone. Being the predominant residues mainly in milk, EFSA proposes that the conjugates of 4-hydroxy diphenylamine should be included in the residue definition for risk assessment as their toxicity is covered by the toxicological assessment of the parent diphenylamine. It should be kept in mind that the residue definition for risk assessment has to be regarded as provisional pending the outcome of the additional data on the nature and magnitude of the residues in apple wet and dry pomace and the recalculation of the livestock dietary burden.

A feeding study on dairy cows was submitted. Upon repeated oral exposure over 28 days to diphenylamine at 3 dose levels (30, 90, 300 mg/animal/day) samples of milk, muscle, liver, kidney and fat were analysed for residues of diphenylamine. According to the livestock dietary burden calculation presented in the addenda of April and July 2008 the highest feeding dose group was considered as appropriate to estimate the residue levels in ruminant tissues and milk in order to derive MRLs. In case ruminants are exposed to diphenylamine residues through diet, transfer of these residues into animal tissue is expected at levels of 0.0074 mg/kg in whole milk, 0.109 mg/kg in fat, 0.257 mg/kg in liver, 0.01 mg/kg in kidney and <0.01 mg/kg in muscle and therefore MRLs have to be set.

If it is concluded that it cannot be excluded that treated apples may become part of livestock diet, the process of the evaluation of the nature and magnitude of residues in livestock will have to be finalised, the outstanding data on the nature and magnitude of the residues in wet and dry pomace will have to be addressed and the livestock dietary burden and the derived MRL proposals for ruminants matrices will have to be revised accordingly.

3.3. Consumer risk assessment

After the PRAPeR 50 experts' meeting on residues, the RMS reconsidered in the addendum of July 2008 the consumer risk assessment taking into account the ADI of 0.075 mg/kg bw agreed during PRAPeR 49 on mammalian toxicology. The refined assessment using the STMR value of 2.39 mg/kg demonstrated that the intakes for all considered consumer groups included in the EFSA PRIMo model are below the proposed ADI, the maximum IEDI being 38.6% of the ADI (DE child). The contribution to consumer exposure from residues in food of animal origin was in all cases negligible (<1% ADI).

No ARfD was allocated und therefore no acute risk assessment was carried out.

It is noted that the consumer risk assessment could not be finalised due to the uncertainties related to the outstanding data on the nature of the residues in raw and processed apples and the potential presence of nitrosamines in these matrices. Moreover, it is not excluded that toxicological reference values may need to be allocated to nitrosamines if it is demonstrated that they occur in raw and/or processed apples and that a consumer exposure assessment for these compounds is needed.

3.4. Proposed MRLs

For the representative use on apples treated with diphenylamine by drench application, a MRL of 7 mg/kg is proposed. This MRL proposal has to be regarded as provisional pending the outcome of the required storage stability data.

Provisional MRLs for food of animal origin are proposed pending the submission of the outstanding data identified in section 3.2:

Liver	0.3 mg/kg
Meat on a fat basis	0.2 mg/kg
Kidney	0.01 mg/kg
Whole milk	0.01* mg/kg (LOQ of the analytical method used in the feeding study).

4. Environmental fate and behaviour

No information with respect to fate and behaviour in the environment was provided in the resubmission dossier.

4.1. Fate and behaviour in soil

4.1.1. Route of degradation in soil

Studies were not provided to address the route of degradation of diphenylamine in soil using the justification that for the applied for intended use, as described, soil exposure will not occur. The peer review accepted this justification was appropriate as when management measures tailored to local practice and legislation were in place, these could effectively exclude soil exposure.

4.1.2. Persistence of the active substance and their metabolites, degradation or reaction products

Studies were not provided to address the rate of degradation of diphenylamine in soil using the justification already outlined above in section 4.1.1.

4.1.3. Mobility in soil of the active substance and their metabolites, degradation or reaction products

Studies were not provided to address the adsorption potential of diphenylamine to soil using the justification already outlined above in section 4.1.1.

4.2. Fate and behaviour in water

4.2.1. Surface water and sediment

Diphenylamine has a water solubility of 25.8 mg/L at 20°C without indications that solubility is pH dependent at environmentally relevant pH; it is therefore considered moderately soluble. Data indicate that diphenylamine is stable to aqueous hydrolysis but undergoes rapid direct aqueous photolysis with an estimated first order DT_{50} of 4.39 hours when equated to summer sunlight equivalents at 40°N (very low persistence at 40°N in the summer). Four major photolysis breakdown products (D1[11], D2[12] and D3 isomers I[13] and II[14]) were identified, with the D3 isomers being stable under aqueous photolysis conditions. A ready biodegradability study (OECD 301D) indicated diphenylamine should be classified as 'not readily biodegradable'. An aerobic laboratory sediment water study was not provided. An aquatic exposure assessment was presented in the DAR, the aim of which was to address potential surface water concentrations that might result as a consequence of disposal of spent treatment solution or accidental spillage during treatment operations. The peer review did not accept that the calculations presented for diphenylamine would cover all possible waste disposal or accidental spillage situations that might result in all apple storage facilities in all Member States. As a consequence the photolysis metabolite levels calculated for surface water presented in the DAR were also concluded as not appropriate. The peer review did however agree that when management measures tailored to local practice and legislation were in place, exposure of surface water could be excluded as a consequence of the applied for intended use. One Member State indicated that they would need to have additional data so they could identify which management measures could be recommended as best practice for addressing disposal and spillage issues. However the Member States agreed that disposal of spent treatment solution or accidental spillage lay outside the regulatory framework and decision making procedures prescribed under the plant protection products authorisations directive.

[11] D1: 9*H*-carbazole
[12] D2: 4-(phenylamino)phenol
[13] D3 isomer I: 3,4-dihydrocyclopenta[*b*]indol-7-ol
[14] D3 isomer II: 1,4-dihydrocyclopenta[*b*]indol-7-ol

4.2.2. Potential for ground water contamination of the active substance their metabolites, degradation or reaction products

Information on the route and rate of degradation and adsorption of diphenylamine in soil is not available, so usual regulatory practice for assessing the potential for groundwater exposure could not be followed. However the peer review accepted that when management measures tailored to local practice and legislation were in place, as these could effectively exclude soil and surface water exposure, this would also exclude the potential for groundwater exposure.

4.3. Fate and behaviour in air

On the basis of measured vapour pressure of diphenylamine ($4.9x10^{-2}$ Pa at 20°C) diphenylamine would be classified under the national scheme of the Netherlands as moderately volatile. However significant concentrations in air would not be expected as this property will be counteracted by its moderate water solubility (25.8 mg/L at 20°C, Henry's Law constant 0.321 Pa m^3 mol^{-1}). Calculations using the method of Atkinson for indirect photooxidation in the atmosphere through reaction with hydroxyl radicals gave an atmospheric half-life estimated at 39 minutes (assuming an atmospheric hydroxyl radical concentration of $1.5x10^6$ radicals cm^{-3}). This indicates that the proportion of applied diphenylamine that will volatilise is unlikely to be subject to long range atmospheric transport.

5. Ecotoxicology

Diphenylamine was discussed in the meeting of experts on ecotoxicology (PRAPeR 48) in May 2008. The representative use evaluated is indoor drenching of apples. No information with respect to ecotoxicology was provided in the resubmission dossier.

5.1. Risk to terrestrial vertebrates

Diphenylamine is of low acute and short-term dietary toxicity to birds and not acutely toxic to mammals. Exposure of birds and mammals is unlikely to occur if diphenylamine is applied according to the proposed GAP. The risk to birds and mammals is considered to be low for the representative use of diphenylamine.

5.2. Risk to aquatic organisms

Diphenylamine is very toxic to aquatic organisms. Exposure of the aquatic environment is considered negligible. The solution used for drenching of apples is collected and recycled. A risk assessment was conducted assuming that 1% of the drenching solution is spilt and enters surface waters via the drainage system. The resulting TERs were above the Annex VI triggers of 100 and 10. This scenario does not cover all possible situations of spillage or disposal of the drenching solution, and no data were provided to assess the risk for the photolysis metabolites that have the potential to be produced in aquatic environments should diphenylamine reach them. However the Member States agreed during the peer review that this lies outside the regulatory framework and decision making procedures prescribed under the plant protection products authorisations directive (see point 4.2.1). Overall it is concluded that the risk to the aquatic environment is considered to be low for the representative use provided that appropriate management practices regarding disposal of the drenching solution and preventing spillage are in place to preclude release to the natural environment.

5.3. Risk to bees

No data were made available on the toxicity of diphenylamine to bees. Exposure of bees is considered to be negligible for the representative use evaluated and hence no studies are considered necessary.

5.4. Risk to other arthropod species

No data were made available on the toxicity of diphenylamine to non-target arthropods. Exposure of non-target arthropods is considered to be negligible for the representative use evaluated and hence no studies are considered necessary.

5.5. Risk to earthworms

No data were made available on the toxicity of diphenylamine to earthworms. Exposure of earthworms is considered to be negligible for the representative use evaluated and hence no studies are considered necessary (see point 4.1.1.).

5.6. Risk to other soil non-target macro-organisms

No data were made available on the toxicity of diphenylamine to soil non-target macro-organisms. Exposure of soil dwelling organisms is considered to be negligible for the representative use evaluated and hence no studies are considered necessary (see point 4.1.1.).

5.7. Risk to soil non-target micro-organisms

No data were made available on the toxicity of diphenylamine to soil non-target micro-organisms. Exposure of soil dwelling organisms is considered to be negligible for the representative use evaluated and hence no studies are considered necessary (see point 4.1.1.).

5.8. Risk to other non-target-organisms (flora and fauna)

No data were made available on the toxicity of diphenylamine to non-target plants. Exposure of non-target plants is considered to be negligible for the representative use evaluated and hence no studies are considered necessary.

5.9. Risk to biological methods of sewage treatment

The respiration of activated sewage sludge was affected by <50% at the highest tested dose of 1000 mg a.s./L (EC_{50} > 1000 mg a.s./L). Entry of diphenylamine into sewers has been considered as being prevented by the management practices that need to be in place. Therefore the risk to biological methods of sewage treatment should be low when these management practices are effective (see point 4.1.1.)

6. Residue definitions

Soil

Definition for risk assessment: Not required as it was accepted that when the representative use is managed appropriately, soil exposure could be precluded.

Definition for monitoring: diphenylamine

Water

Ground water

Definition for exposure assessment: Not required as it was accepted that when the applied for intended use was managed appropriately, groundwater exposure could be precluded.

Definition for monitoring: diphenylamine

Surface water

Definition for risk assessment: Not required as it was accepted that when the applied for intended use was managed appropriately, surface water and sediment exposure could be precluded.

Definition for monitoring: diphenylamine, D3 isomer I and D3 isomer II

Air

Definition for risk assessment: diphenylamine

Definitions for monitoring: diphenylamine

Food of plant origin

Definition for risk assessment: diphenylamine, provisional until metabolites/degradation products in raw and processed apples have been fully identified. This is also related to the potential presence of nitrosamines (for details refer to section 3.1.1).

Definition for monitoring: diphenylamine.

Food of animal origin

Definition for risk assessment: diphenylamine and conjugates of 4-hydroxy-diphenylamine, provisional pending on the nature and magnitude of the residues in apple wet and dry pomace and the recalculation of the livestock dietary burden (for details refer to section 3.2 of this document)

Definition for monitoring: diphenylamine.

7. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments

7.1. Soil

Compound (name and/or code)	Persistence	Ecotoxicology
None, but diphenylamine in case of spillage and accident.	No data available for diphenylamine, exposure precluded by appropriate management of the application practice.	No data available for diphenylamine. No data necessary if exposure can be precluded.

7.2. Ground water

Compound (name and/or code)	Mobility in soil	>0.1 µg/L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological activity
None, but diphenylamine in case of spillage and accident.	No data available	No	Diphenylamine yes	Diphenylamine yes	Diphenylamine yes

7.3. Surface water and sediment

Compound (name and/or code)	Ecotoxicology
None, but diphenylamine in case of spillage and accident.	Very toxic to aquatic organisms. However exposure is considered negligible.
None, but D3 isomer I and D3 isomer II in case of spillage and accident.	No data available for D3 isomer I and D3 isomer II. However exposure is considered negligible.

7.4. Air

Compound (name and/or code)	Toxicology
diphenylamine	Not technically feasible to perform an acute toxicity study by inhalation.

8. List of studies to be generated, still ongoing or available but not peer reviewed

- A detailed specification of the starting material (relevant for all uses, data gap identified by meeting of experts May 2008, date of submission unknown, refer to section 1).
- Method of analysis for D3 isomers in surface water (relevant for all uses, data gap identified by EFSA September 2008, date of submission unknown, refer to section 1).
- Method of analysis for products of animal origin (relevant for all uses, data gap identified by EFSA July 2008, date of submission unknown, refer to section 1).
- The identity and toxicological profile of metabolites coded 1, 2 and 3 present in significant amounts in treated apples should be clarified (relevant for the representative use evaluated; data gap identified by meeting of experts in June 2008; refer to sections 2.8 and 3.1.1).
- A study investigating the nature of the residues in apple processed commodities under the standard hydrolytic conditions representative of pasteurisation, baking and cooking and sterilisation (relevant for the representative use evaluated; data gap identified by meeting of experts in June 2008; refer to section 3.1.1).
- The applicant should investigate the potential presence of nitrosamines in apple raw and processed commodities, including a toxicological assessment (relevant for the representative use evaluated; data gap identified by meeting of experts in June 2008 refer to sections 2.8 and 3.1.1).
- Clarification on the results from the processing studies with regard to residue levels for wet and dry pomace is required (relevant for the representative use evaluated; data gap identified by meeting of experts June 2008; refer to section 3.2).
- Additional storage stability data are required to cover the maximum storage time interval of the samples from the supervised residue trials in apples (relevant for the representative use evaluated; data gap identified during resubmission; refer to section 3.1.1).

CONCLUSIONS AND RECOMMENDATIONS

OVERALL CONCLUSIONS

The representative formulated product for the evaluation was "No Scald DPA 31", an emulsifiable concentrate (EC).

Adequate methods are available to monitor all compounds given in the respective residue definition, except for surface water and products of animal origin. Residues in food of plant origin can be determined with a multi-method (the German S19 method has been validated). For the other matrices only single methods are available to determine residues of diphenylamine. A data gap is identified for a method of analysis for products of animal origin and for surface water.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

In the mammalian metabolism studies, diphenylamine was rapidly and completely absorbed after oral administration, it underwent extensive metabolism to sulphonyl and glucuronyl conjugates and was rapidly excreted mainly via urine. Acute oral and dermal toxicity were low, it was not technically feasible to perform an acute toxicity study by inhalation. Diphenylamine was not a skin irritant, but

can cause severe irritation to the eyes; therefore, classification with Xi "irritant" and risk phrase R41 "risk of serious damage to eyes" was proposed. According to a Magnusson and Kligman test, diphenylamine was not a skin sensitizer.

The red blood system was the target organ of diphenylamine in rats, mice and dogs, upon short-term and long-term exposure, as evidenced by altered haematological parameters, splenic erythropoiesis, splenic congestion and haemosiderosis. Additionally, histopathological changes in the liver and kidneys were found upon longer exposure. The relevant short-term NOAEL of 9.6 - 10 mg/kg bw/day was derived from the 90-day rat, 90-day dog and 1-year dog studies. The relevant long-term NOAEL was the dose level of 7.5 mg/kg bw/day from the 2-year rat study.

No genotoxic potential was attributed to diphenylamine; no carcinogenicity was observed in either rats or mice. Reproductive effects were limited to reduced implantation sites in F_1 females associated with reduced litter size at clear parental toxic doses (reduced food intake/body weight gain and haemolytic condition). No effect on development was attributed to diphenylamine administration in rat or rabbit.

No neurotoxic alert was evident in the data package provided.

The Acceptable Daily Intake (ADI) of diphenylamine was 0.075 mg/kg bw/day, the Acceptable Operator Exposure Level (AOEL) was 0.1 mg/kg bw/day and no Acute Reference Dose (ARfD) was allocated. As no study was provided, default dermal absorption value of 100 % was assumed for risk assessment. The level of operator exposure calculated for the representative formulation No Scald DPA 31 was below the AOEL according to the mixing and loading phase of the German model when operators wear gloves. Considering the very specific indoor use of diphenylamine, bystander and re-entry worker exposure were not considered relevant. The worker exposure (interpreted as sorting out and packaging fruits activities) risk assessment relates to the automated handling of the treated fruits; manual handling of the fruits has not been taken into consideration.

The metabolism of diphenylamine was investigated in apples at different time intervals after a post-harvest treatment by dipping. Over the course of the study a penetration of the radiolabelled residues was observed from the surface of the fruit into the pulp. Upon analysis diphenylamine was always the major residue, however identification of metabolites was considered insufficient by the meeting of experts and therefore a data gap was set to address mainly the identity of the metabolites coded 1, 2 and 3 detected in significant amounts in the apple samples. Also the potential for presence or formation of nitrosamines in apple metabolism or during processing is not excluded and has to be investigated according to a fully validated analytical method. This data gap is linked to the data gap set to address the nature of the residues in the apple processed commodities. The residue definition for monitoring was set as diphenylamine alone whilst the residue definition for risk assessment could only provisionally be proposed as the parent compound pending the outcome of the additional data to address the identity of the metabolites 1, 2 and 3 and also the potential presence of nitrosamines both in apple extracts and in the processed commodities.

Livestock metabolism and feeding studies in ruminants were evaluated and considered as acceptable. The applicant made a case that treated apples are destined only for direct human consumption and will not be part of livestock diet. However, since any restriction with respect to the use of treated apples or commodities derived from treated apples in animal feeding is not in the remit of the risk assessor, a "worst case" assessment has to be carried out assuming livestock exposure to diphenylamine residues from treated apples in order to derive MRLs for animal matrices. The residue definition for monitoring was set as diphenlyamine alone, while for risk assessment EFSA proposed to include both diphenylamine and the conjugates of 4-hydroxy diphenylamine since these metabolites were found to be predominant in milk. The residue definition for risk assessment has to be regarded as provisional pending the outcome of the requested additional data on the nature and magnitude of the residues in apple wet and dry pomace and the recalculation of the livestock dietary burden.

The consumer risk assessment is not finalised due to the identified data gaps on the identity and toxicological profile of metabolites coded 1, 2, and 3 in raw apples, the nature of the breakdown

products under processing conditions, the potential occurrence of nitrosamines in raw and processed apples and the storage stability of diphenylamine residues in the residue trials samples.

The only data available in the dossier that were pertinent to the fate and behaviour of diphenylamine in the environment were the results of water solubility, direct aqueous photolysis and vapour pressure experiments and indirect photooxidation in the atmosphere through reaction with hydroxyl radicals. However it was concluded that despite these limited data, as a consequence of the applied for intended use of diphenylamine when combined with management measures tailored to local practice and legislation regarding disposal and preventing spillage being in place, this information was sufficient to characterise the environmental risk at the EU level as exposure of soil, surface water and sediment and consequently groundwater would be expected to be negligible. Though diphenylamine is moderately volatile, significant concentrations in air would not be expected as this property will be counteracted by its water solubility. Diphenylamine would not be expected to have the potential for long range atmospheric transport due to its expected potential for indirect photochemical oxidative degradation in the atmosphere.

Exposure of birds and mammals from the representative use as an indoor drench treatment of apples is considered unlikely. Diphenylamine is very toxic to aquatic organisms. However exposure of aquatic organisms is considered to be negligible. No data were made available for other non-target organisms. However exposure of non-target organisms is assumed to be unlikely if the product is applied according to the GAP and studies are considered unnecessary. The risk to biological methods of sewage treatment was assessed as low when the exposure via sewers is appropriately managed.

9. Particular conditions proposed to be taken into account to manage the risk(s) identified

- It is likely that when product containers are opened diphenylamine is degraded and therefore appropriate labelling should be considered.

- Some tank mixes may result in the formation of nitrosamines therefore these should be carefully assessed on a case-by-case basis (refer to point 3.1.1).

- Operator exposure was estimated to be below the AOEL when gloves are worn, according to the mixing and loading phase of the German model (refer to point 2.12).

- The worker exposure (interpreted as sorting out and packaging fruits activities) risk assessment relates to the automated handling of the treated fruits; manual handling of the fruits has not been taken into consideration (refer to point 2.12).

- The risk to soil and aquatic organisms is characterised as low and the potential for groundwater contamination is considered low but only as exposure of the natural environment is precluded in these assessments. Therefore management measures tailored to local practice and legislation need to be put in place to control the waste disposal of spent application solution and prevent accidental spillage entering sewers or surface water drains. (Member States indicated that they may wish to have additional environmental data to support and inform the management measures that they have to put in place. For example the proposal made in the DAR (section B.8.4.4) that holding the solution in lagoons to allow photolysis to degrade diphenylamine before being applied to soil, may be ill advised in the absence of any soil degradation or mobility data, or data on effects on soil-dwelling organisms of the known aqueous photodegradation products).

- Only the use with drench application has been considered in the peer review. The use with dipping application, no longer supported for the peer review, was not assessed, but there are indications that this use will lead to higher residues in apples treated at the same application rate that has been assessed for the drench application.

10. Concerns

10.1. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles of Annex VI to Directive 91/414/EEC and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

1. The consumer risk assessment is not finalised due to the identified data gaps on the identity and toxicological profile of the metabolites coded 1, 2, and 3 in raw apples, the nature of the breakdown products under processing conditions, the potential occurrence of nitrosamines in raw and processed apples and the storage stability of diphenylamine residues in the residue trials samples.

10.2. Critical areas of concern

An issue is listed as a critical area of concern where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles of Annex VI to Directive 91/414/EEC, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

No critical areas of concern were identified.

10.3. Overview of the concerns for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in section 9, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)

Representative use		**Apples**
Operator risk	Risk identified	
	Assessment not finalised	
Worker risk	Risk identified	
	Assessment not finalised	
Bystander risk	Risk identified	
	Assessment not finalised	
Consumer risk	Risk identified	
	Assessment not finalised	X[1]
Risk to wild non target terrestrial vertebrates	Risk identified	
	Assessment not finalised	
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified	
	Assessment not finalised	
Risk to aquatic organisms	Risk identified	
	Assessment not finalised	
Groundwater exposure active substance	Legal parametric value breached	
	Assessment not finalised	
Groundwater exposure metabolites	Legal parametric value breached	
	Parametric value of 10µg/L[(a)] breached	
	Assessment not finalised	
Comments/Remarks		

The superscript numbers in this table relate to the numbered points indicated within section 10.1 and 10.2. Where there is no superscript number, see sections 2 to 6 for more explanation.

(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

REFERENCES

EFSA (European Food Safety Authority), 2008a. Conclusion regarding the peer review of the pesticide risk assessment of the active substance diphenylamine. EFSA Scientific Report (2008) 188.

EFSA (European Food Safety Authority), 2008b. Peer Review Report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance diphenylamine.

EFSA (European Food Safety Authority), 2011. Peer Review Report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance diphenylamine.

European Commission, 1999. Guidelines for the generation of data concerning residues as provided in Annex II, part A, section 6 and Annex III, part A, section 8, of Directive 91/414/EEC concerning the placing of plant protection products on the market, 1607/VI/97 rev. 2, 10/6/1999.

European Commission, 2000. Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414. SANCO/3030/99 rev.4, 11 July 2000.

European Commission, 2003. Guidance document on assessment of the relevance of metabolites in groundwater of substances regulated under council directive 91/414/EEC. SANCO/221/2000-rev 10-final, 25 February 2003.

European Commission, 2004a. Guidance document on residue analytical methods. SANCO/825/00 rev. 7, 17 March 2004.

European Commission, 2004b. Guidance Document on Dermal Absorption. SANCO/222/2000 rev. 7, 19 March 2004.

European Commission, 2009a. Guidance Document on the Assessment of the Equivalence of Technical Materials of Substances Regulated under Council Directive 91/414/EEC. SANCO/10597/2003 – rev. 8.1, May 2009.

European Commission, 2009b. Review Report for the active substance diphenylamine finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 26 February 2009 in support of a decision concerning the non-inclusion of diphenylamine in Annex I of Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance. SANCO/191/08-final, 1 December 2009.

European Commission, 2011. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. SANCO Doc 7525/VI/95-rev.9.

Ireland, 2007. Draft Assessment Report (DAR) on the active substance diphenylamine prepared by the rapporteur Member State Ireland in the framework of Directive 91/414/EEC, May 2007.

Ireland, 2008. Final Addendum to Draft Assessment Report on diphenylamine, compiled by EFSA, July 2008.

Ireland, 2010. Additional Report to the Draft Assessment Report on the active substance diphenylamine prepared by the rapporteur Member State Ireland in the framework of Commission Regulation (EC) No 33/2008, November 2010.

Ireland, 2011. Final Addendum to the Additional Report on diphenylamine, compiled by EFSA, July 2011.

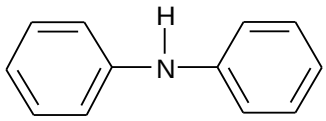
APPENDICES

APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Common name: Diphenylamine (Not an ISO name).
Function (*e.g.* fungicide)	Plant growth regulator.
Rapporteur Member State	Ireland.
Co-rapporteur Member State	None.

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	Diphenylamine
Chemical name (CA) ‡	N-phenylbenzenamine
CIPAC No ‡	460.
CAS No ‡	122-39-4
EC No (EINECS or ELINCS) ‡	204-539-4
FAO Specification (including year of publication) ‡	None.
Minimum purity of the active substance as manufactured ‡	987 g/kg
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Aniline max. level 5 mg/kg 4-aminobiphenyl max. level 2 mg/kg 2-aminobiphenyl 6.5 mg/kg
Molecular formula ‡	$C_{12}H_{11}N$
Molecular mass ‡	169.23 g/mol
Structural formula ‡	

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	53 – 54°C (purity 99%)
Boiling point (state purity) ‡	298.8°C (purity 100%)
Temperature of decomposition (state purity)	Not applicable
Appearance (state purity) ‡	Pure material: cream crystalline solid (99%)
	Technical material: not given.
Vapour pressure (state temperature, state purity) ‡	8.52 x 10-2 Pa at 25°C (99.4%)
Henry's law constant ‡	0.321 $Pa.m^3.mol^{-1}$ (Vapour pressure data determined at 25°C, 35°C and 45°C was extrapolated to 20°C as 4.90 x 10^{-2} Pa.)
Solubility in water (state temperature, state purity and pH) ‡	25.8 mg/L at 20°C in distilled Milli-RO water (pH ca.7.5) (99%)
Solubility in organic solvents ‡ (state temperature, state purity)	Solubility at 20°C in g/L (99%) n-hexane: 33 - 40 toluene: 667 - 1000 dichloromethane: >1000 methanol: 400 - 500 acetone: >1000 ethyl acetate: >1000
Surface tension ‡ (state concentration and temperature, state purity)	71.8 mN/m at 20 °C (90 % saturated solution)(99%)
Partition co-efficient ‡ (state temperature, pH and purity)	log $K_{O/W}$ = 3.82 at 20 °C (pH 7)(99%)
	Effect of pH was investigated and no noticeable change was found. log $K_{O/W}$ = 3.71 at 20 °C (pH 4)(99%) log $K_{O/W}$ = 3.82 at 20 °C (pH 7)(99%) log $K_{O/W}$ = 3.81 at 20 °C (pH 9)(99%) Milli-RO water = 3.84 at 20 °C.
Dissociation constant (state purity) ‡	The spectrophotometric technique for determining pKa values is designed for the pH range of 2-12. Because the pKa of diphenylamine is <2, the pKa results were reported as an estimated pKa value. The average estimated pKa value of diphenylamine for three trials in 4.75% ethanol/water is 1.03 at 20°C (>99% purity).

UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	λ_{max} was determined at 284 nm with a second band at 204 nm. At 284 nm the $\log_{10}$ ε was 4.32 (methanol), 4.57 (acidified methanol) and 4.37 (basic methanol). At 204 nm the $\log_{10}$ ε was 4.49 (methanol), 4.75 (acidified methanol) and 4.37 (basic methanol).
Flammability ‡ (state purity)	The test substance is not flammable (100%). Auto-flammability: no ignition was detected at temperatures below 400°C, the upper limit of the test. The test substance does not ignite below the melting point.
Explosive properties ‡ (state purity)	Not explosive (100%).
Oxidising properties ‡ (state purity)	Not oxidising (100%).

Summary of representative uses evaluated (diphenylamine)*.

Crop and/ or situation (a)	Member State, Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min/ max (k)	interval between applications (min – max)	kg as/hL min – max	water L/ha min – max	kg as/ha min – max		
Apples	Northern & Southern Europe	No Scald DPA 31	I	Scald	EC	318 g/l	Drenching	Applied within 7 days of harvesting	1	N/A	0.04 – 0.2 (0.13 – 0.63 L/hL)	N/A	N/A	N/A	

Uses should be crossed out when the applicant no longer supports this use(s).

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	HPLC-UV
Impurities in technical as (analytical technique)	Relevant impurities: HPLC-EC (electrochemical detector)
Plant protection product (analytical technique)	HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Diphenylamine.
Food of animal origin		Diphenylamine.
Soil		Diphenylamine.
Water	surface	Diphenylamine, D3 isomer I, D3 isomer II
	drinking/ground	Diphenylamine.
Air		Diphenylamine.

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Multiresidue method A multiresidue method is available [DFG S19]. LOQ = 0.05 mg/kg
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Open
Soil (analytical technique and LOQ)	LC/MS/MS LOQ (sandy soil): 0.01 mg/kg LOQ (clay soil): 0.01 mg/kg
Water (analytical technique and LOQ)	LC/MS/MS LOQ (ground water/tap water): 0.02 µg /l LOQ (surface water): 0.05 µg /l OPEN for 3,4-dihydrocyclopenta[*b*]indol-7-ol and 1,4-dihydrocyclopenta[*b*]indol-7-ol
Air (analytical technique and LOQ)	LC/MS/MS LOQ: 0.0025 mg/m^3 air
Body fluids and tissues (analytical technique and LOQ)	LC/MS/MS LOQ (human plasma): 0.05 mg/L Open for tissues, which is covered by a data gap for products of animal origin.

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

	RMS/peer review proposal
Active substance	Does not classify from a physical/chemical point of view.

Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1)

Rate and extent of oral absorption ‡	Rapidly absorbed, > 79 % within 48 hours (based on excretion via urine and tissue content)
Distribution ‡	Narrow distribution, highest residues associated with the liver, blood and residual carcass
Potential for accumulation ‡	Unlikely
Rate and extent of excretion ‡	At all dosage levels the major route of elimination in rats is via the urine for both sexes (72 – 89 %), in addition, females tend to excrete a higher amount in faeces than males for the low dose groups while the reverse is true for high dose administration of DPA
Metabolism in animals ‡	Extensively metabolised, > 84 % (13 metabolites including parent identified); 4-OH-DPA was the major free metabolite detected in both urine and faeces and parent is found in small amounts in faeces
Toxicologically relevant compounds ‡ (animals and plants)	Diphenylamine
Toxicologically relevant compounds ‡ (environment)	Diphenylamine

Acute toxicity (Annex IIA, point 5.2)

Rat LD50 oral ‡	> 15000 mg/kg bw	
Rabbit LD50 dermal ‡	> 7500 mg/kg bw	
Rat LC50 inhalation ‡	No data, study was not technically feasible to perform	
Skin irritation ‡	Not irritant	
Eye irritation ‡	Severe irritant	**R41**
Skin sensitisation ‡	Non-sensitiser (Magnusson & Kligman)	

Short-term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	RBC; Splenic congestion and haemosiderosis; extramedullary haematopoiesis; clinical chemistry (dog, rats and mice)	
Relevant oral NOAEL ‡	1-year dog + 90-day dog: 10 mg/kg bw/day 90-day rat: 9.6 mg/kg bw/day 90-day mouse: 1.7 mg/kg bw/day (with a LOAEL of 94 mg/kg bw/day)	
Relevant dermal NOAEL ‡	21-day rabbit: 100 mg/kg bw/day	
Relevant inhalation NOAEL ‡	No data - not required	

Genotoxicity ‡ (Annex IIA, point 5.4)

	No genotoxic potential	

Long-term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	Red blood cell, splenic congestion with haemosiderosis, and histopathological changes in the spleen, kidney and liver (rat and mouse).	
Relevant NOAEL ‡	7.5 mg/kg bw/day (2-year rat study) LOAEL: 73.2 mg/kg bw/day (18-month mouse)	
Carcinogenicity ‡	No carcinogenic potential	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Maternal: haematological parameters changes / histological findings in liver and spleen Offspring: decreased pup weight at maternally toxic doses Reproductive: ↓implantation sites at maternally toxic dose	
Relevant parental NOAEL ‡	LOAEL: 32 mg/kg bw/day	
Relevant reproductive NOAEL ‡	92 mg/kg bw/day	
Relevant offspring NOAEL ‡	32 mg/kg bw/day	

Developmental toxicity

Developmental target / critical effect ‡	Maternal: histopathology (rat) Decreased body weight gain and food consumption (rabbit) Developmental: no foetal findings attributed to treatment (rat and rabbit)	
Relevant maternal NOAEL ‡	Rat: 50 mg/kg bw/day Rabbit: 100 mg/kg bw/day	
Relevant developmental NOAEL ‡	Rat: 100 mg/kg bw/day Rabbit: 300 mg/kg bw/day	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data - not required	
Repeated neurotoxicity ‡	No data - not required	
Delayed neurotoxicity ‡	No data - not required	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	No data - not required
Studies performed on metabolites or impurities ‡	No data - open issue pending on the identification and quantification of metabolites and potential presence of nitrosamines in the residues relevant for consumer exposure.

Medical data ‡ (Annex IIA, point 5.9)

No toxic effects reported in plant personnel.

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.075 mg/kg bw/day	2-year rat	100
AOEL ‡	0.1 mg/kg bw/day	90-day/one-year dog and 90-day rat	100
ARfD ‡	Not allocated	-	-

Dermal absorption ‡ (Annex IIIA, point 7.3)

Formulation: NO SCALD DPA 31 (318 g diphenylamine/L EC)	No data, default value of 100 %

Exposure scenarios (Annex IIIA, point 7.2)

Operator	The estimated exposure from NO SCALD DPA 31 according to the German model (mixing/loading only) for drive through drench/automated bin drench, at max. treatment volume of 2000 L/day and max. diphenylamine concentration of 2 g/L is below the AOEL when gloves are worn. German model (mix/load) — % of AOEL Without PPE — 160 % With PPE (gloves) — 1.6 %
Workers	Not relevant for the proposed uses, re-entry workers activities are not applicable, automated sorting out and packaging of apples considered
Bystanders	Not relevant for the proposed uses

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

RMS/peer review proposal

Substance classified: diphenylamine	**Xi** "Irritant" **R41** "Risk of serious damage to eyes"

Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Apples – post harvest treatment-drenching
Rotational crops	Not relevant for post harvest use.
Metabolism in rotational crops similar to metabolism in primary crops?	Not relevant.
Processed commodities	Data gap identified for a new study addressing the nature of the residues in processed commodities according to the standard hydrolytic conditions.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Open: see data gap above
Plant residue definition for monitoring	Diphenylamine
Plant residue definition for risk assessment	Diphenylamine – **Provisional** - pending the identification of metabolites coded 1, 2 and 3 in raw apples, the breakdown and reaction products in processed commodities and the determination of the potential nitrosamines both in raw apples and processed commodities.
Conversion factor (monitoring to risk assessment)	Open

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Goat, hens
Time needed to reach a plateau concentration in milk and eggs	Unable to conclude on a 7-day dosing period.
Animal residue definition for monitoring	Diphenylamine
Animal residue definition for risk assessment	Diphenylamine and conjugates of 4-OH-diphenylamine. – **Provisional** – pending the nature and magnitude of the residues in apple wet and dry pomace and the recalculation of the dietary burden.
Conversion factor (monitoring to risk assessment)	Open – Pending finalisation of the residue definition for risk assessment.
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	Yes (log $P_{O/W}$ > 3).

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Not relevant for post-harvest use.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

Residues of diphenylamine are stable under frozen storage conditions for up to 5 months in whole apple and pomace and for up to 7 months in apple juice. Data gap identified to provide storage stability data to cover the maximum period of storage of the samples from the residue trials (260 days).

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Ruminant:	Poultry:	Pig:
Conditions of requirement of feeding studies		

Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	Yes[15] Dairy cattle: 6.26 mg/kg feed DM (125 mg/cow/day) Beef cattle: 18.8 mg/kg feed DM (281 mg/cow/day)	N/A	N/A
Potential for accumulation (yes/no):	Yes	N/A	N/A
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	Yes	N/A	N/A
	Relevant dosing group in the feeding study: 300 mg diphenylamine/cow/day Overdosing factor: -Dairy cattle: 2.5N -Beefcattle: 1N Residue levels in matrices: Mean (max) mg/kg[16]		
Muscle	<0.01[17]	[2] N/A	[2] N/A
Liver	0.257	[2] N/A	[2] N/A
Kidney	0.010	[2] N/A	[2] N/A
Fat	0.109	[2] N/A	[2] N/A
Milk	0.0074		
Eggs		[2] N/A	

[1] State whether intake by specified animals is ≥ 0.1 mg/kg diet/day or not, based on a dry weight basis as given in table 1 of Guidance Document Appendix G

[2] Fill in results from appropriate feeding studies at appropriate dose rates according to Guidance Document Appendix G. State 'not required' when the conditions of requirement of feeding studies according to directive 91/414/EEC are not met.

[15] The assessment was based on the worst-case assumption that treated apples could be part of livestock diet. The intake has to be regarded as provisional pending the nature and the magnitude of the residues in apple pomace.

[16] Highest residue levels recovered in muscle, liver, kidney, fat and average residue level in milk at the feeding dose rate of 300 mg/animal/day (2.5 N and 1 N for dairy and beef cattle, respectively).
N/A: not applicable.

[17] LOQ of the analytical method used in the feeding study.
N/A: not applicable.

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses[18] (a)	Recommendation/ comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Apples	N & S Indoor application. Drenching application. Applied within 7 days of harvesting. 0.2 kg as/hl.	**Drench application:** There are 5 different apple trials, which support the supplied GAP. The following residues were found: 1.19, 1.32, 2.39, 2.44 and 3.37 mg/kg		MRL = 7 mg/kg (for drench application)	3.37	2.39 Rmax=6.61 Rber=6.21

(a) Numbers of trials in which particular residue levels were reported *e.g. 1x* mg/kg
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use
(c) Highest residue

[18] Acceptability of these residue trials is pending additional storage stability data to cover the maximum storage period of the samples from the residue trials (260 days).

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8) [19]

ADI	0.075 mg/kg bw/day
TMDI (% ADI) according to EFSA PRIMo rev.2A	113% ADI (DE child)
IEDI (% ADI) according to EFSA PRIMo rev.2A	38.6% (DE Child) 20.6% (NL Child) 8.94% (FR Toddler)
Factors included in IEDI	The STMR on raw apples: 2.39 mg/kg
ARfD	Not allocated.
IESTI (% ARfD)	Not applicable.
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not applicable.
Factors included in IESTI and NESTI	Not applicable.

[7] To be done on the basis of WHO guidelines and recommendations with the deviations within the EU so far accepted (especially diets).

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4) [20]

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Food of plant origin:

Proposed MRLs	7 mg/kg (drench application) Provisional pending the outcome of the storage stability data.

Food of animal origin:

Proposed MRLs*	Whole milk: 0.01* mg/kg Meat (on fat basis): 0.2 mg/kg Liver: 0.3 mg/kg Kidney: 0.01 mg/kg These MRLs are provisional pending the outcome of the data to address the nature and magnitude of the residues in apple wet/dry pomace and the livestock dietary burden calculation.

[19] The consumer risk assessment cannot be finalised due to the following outstanding data: nature of the residues in raw and processed apples, the potential presence of nitrosamines in raw apple and processed matrices and livestock exposure assessment (nature and magnitude of the residues in apple wet/dry pomace).
[20] The processing factors will have to be revised pending the nature of the residues in apple processed commodities.

Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	Not applicable
Non-extractable residues after 100 days ‡	Not applicable
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	Not applicable

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡

Mineralization after 100 days	Not applicable
Non-extractable residues after 100 days	Not applicable
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Not applicable

Soil photolysis ‡

Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Not applicable

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies ‡

Parent	Aerobic conditions: Not applicable

Field studies ‡

Parent:	Aerobic conditions: Not applicable

pH dependence ‡ (yes / no) (if yes type of dependence)	Not applicable
Soil accumulation and plateau concentration ‡	Not applicable

Laboratory studies ‡

Parent:	Anaerobic conditions: Not applicable

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡ Not applicable

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Not applicable
Aged residues leaching ‡	Not applicable
Lysimeter/ field leaching studies ‡	Not applicable

PEC (soil) (Annex IIIA, point 9.1.3)

Parent: Method of calculation	Not applicable
Application data	Not applicable

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	DPA: pH 5: 25 °C, DT_{50} 315.86 d (1^{st} order, r^2 = 0.97163)
	pH 7: 25 °C, DT_{50} 351.55 d (1^{st} order, r^2 = 0.90765)
	pH 9: 25 °C, DT_{50} 358.39d (1^{st} order, r^2 = 0.69195)
Photolytic degradation of active substance and metabolites above 10 % ‡	DPA: Xenon arc lamp (pH 7, 25 °C) DT_{50} 4.39 h (1^{st} order, r^2 = 0.99915) DPA: Xenon arc lamp (distilled water, 20 °C) DT_{50} 1.31 h (1^{st} order, r^2 = 0.976), corresponding to a DT_{50} value in sunlight equivalents of 4.39 h at 40 °N latitude. At equivalent sunlight hours: Model = US EPA GCSOLAR, DT_{50} 1.22 h (40 °N latitude, summer, 100 cm depth) Metabolite: D1: max. formation = 52% after 10.5 hours D2: max. formation = 16% after 36.0 hours D3: max. formation = 93% after 192 hours
Quantum yield of direct phototransformation in water at λ > 290 nm	DPA: Φ = 0.16 (over wavelengths >290 nm)
Readily biodegradable ‡ (yes/no)	DPA: No

Degradation in water / sediment

Parent	Not applicable. No Aerobic water/sediment study provided. Anaerobic water/sediment study (with major methodological deviations) reviewed as supporting information only (see Section B.8.4.3.2) and not required for aquatic risk assessment.

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

DPA Parameters used in FOCUSsw step 1 and 2	FOCUS modelling not applicable for indoor post-harvest treatment. Not calculated
Parameters used in FOCUSsw STEP 3.	FOCUS modelling not applicable for indoor post-harvest treatment.
Application rate	Not applicable
Parameters used in FOCUSsw STEP 4.	Not applicable

PEC (groundwater) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	FOCUS modelling not applicable for indoor post-harvest treatment. Not calculated
Application rate	Not applicable

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not determined – no data requested
Quantum yield of direct phototransformation	see quantum yield of direct phototransformation in water at $\lambda > 290$ nm
Photochemical oxidative degradation in air ‡	DPA: DT_{50} = 0.642 h (0.053 d) (Atkinson method), OH (12 h) concentration assumed = 1.5×10^6 radicals/cm^3 (AOP v1.91)
Volatilisation ‡	from plant surfaces: Not determined
	from soil surfaces: Not determined
Metabolites	Not determined

PEC (air)

Method of calculation	Not calculated. Expected to be negligible based on expert judgement founded on vapour pressure (4.90×10^{-2} Pa at 20°C), Henry's Law Constant (0.321 Pa m^3 mol^{-1}), method of application and photochemical oxidative half-life in air.

$PEC_{(a)}$

Maximum concentration	Not calculated.

Residues requiring further assessment

Environmental occurring residues requiring further assessment by other disciplines (toxicology and ecotoxicology) or for which a groundwater exposure assessment is triggered.	Definition for environmental risk assessment: Soil: Not applicable Groundwater: Not applicable Surface water: Not applicable Sediment: Not applicable Air: diphenylamine only

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	Relevant European data not available
Surface water (indicate location and type of study)	Relevant European data not available
Groundwater (indicate location and type of study)	Relevant European data not available
Air (indicate location and type of study)	Relevant European data not available

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

Candidate for R 53, DPA is not readily biodegradable, with consideration given to Commission Directive 2001/59/EC and 2003/82/EC

Effects on Non-target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds ‡				
Colinus virginianus	DPA Technical	Acute	>2250	-
Anas platyrhynchos	DPA Technical	Short-term	2293	-
Diphenylamine is used for post-harvest applications to control apple scald, applied in indoor situations. Repeated and continuous exposure of birds or their nest sites during the breeding season is therefore not expected and it is proposed that this point is not relevant for Diphenylamine				
Mammals ‡				
Oryctolagus cuniculus	NoScald DPA 31 EC (ATO BAFBC03)	Acute	>15,000	-
Additional higher tier studies ‡				

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Cereals 3 x 80 g a.s../ha.

Indicator species/Category[2]	Time scale	ETE	TER[1]	Annex VI Trigger[3]
Tier 1 (Birds) - late crop growth stage.				
Not applicable due to mode of use-indoor use				
Tier 1 (Mammals) - late crop growth stage.-cereals 2 x 100 g a.s. / ha.				
Not applicable due to mode of use-indoor use				

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg a.s. /L)
Laboratory tests Fish ‡				
Fish				
Oncorhynchus mykiss	DPA Technical	96 hr (flow-through)	Mortality, LC_{50} NOEC	2.2 0.71
Lepomis macrochirus	DPA Super-Refined Diphenylamine	96 hr (flow-through)	Mortality, LC_{50} NOEC	1.46 0.83
No chronic fish tests required				
Aquatic invertebrate				
Daphnia magna	SAN 619F	48 h (flow-through)	Mortality, EC_{50} NOEC	1.2 <0.38

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg a.s. /L)
No chronic aquatic invertebrate tests required				
Sediment dwelling organisms				
No tests required on sediment dwelling organisms				
Algae				
Selenastrum capricornutum	DPA Super-Refined Diphenylamine	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50} NOEC	0.18 0.30 0.04
No tests on higher plants required				
Microcosm or mesocosm tests Not required				

[1] indicate whether based on nominal ($_{nom}$) or mean measured concentrations ($_{mm}$). In the case of preparations indicate whether end points are presented as units of preparation or a.s.

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Not required

Bioconcentration Not required

[1] only required if log $P_{O/W}$ >3.
* based on total ^{14}C or on specific compounds – *total* ^{14}C.

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

No tests on honey bees required

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

No tests on other non-target arthropods required

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

No tests on earthworms, other soil macro-organisms and soil micro-organisms required

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

No tests on other non-target organisms (flora and fauna) required

Additional studies (e.g. semi-field or field studies)

Not required

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	*Unspecified*
Activated sludge	-

End point - 3 hr EC 50	>1000 a.s./L

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

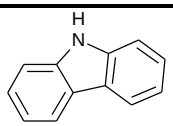
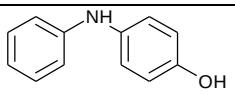
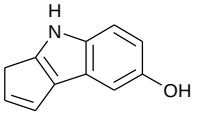
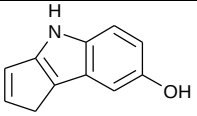
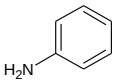
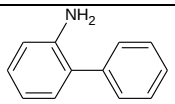
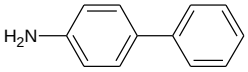
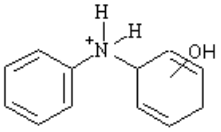
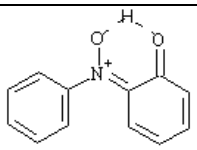
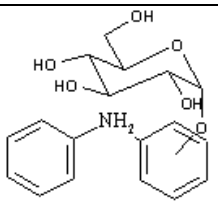
	RMS/ proposal *
SAN 619F	N Dangerous for the environment. R50/53 Very toxic to aquatic organisms, may cause long-term adverse effects in the environment
	S61 Avoid release to the environment. Refer to special instructions /safety data sheets

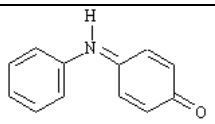
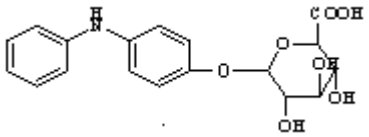
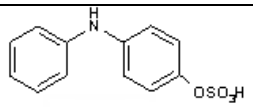
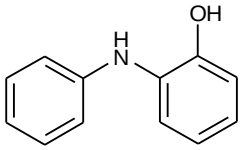
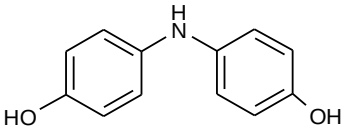
* Reference: Ellgehaussen, 1986

	RMS/ proposal *
SAN 619F SL 100	N Dangerous for the environment. R50/53 Very toxic to aquatic organisms, may cause long-term adverse effects in the environment
	S61 Avoid release to the environment. Refer to special instructions /safety data sheets

* Reference : Jenkins 1990 f

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
D1	9*H*-carbazole	
D2 4-hydroxy diphenylamine 4-OH-diphenylamine	4-(phenylamino)phenol	
D3 isomer I	3,4-dihydrocyclopenta[*b*]indol-7-ol	
D3 isomer II	1,4-dihydrocyclopenta[*b*]indol-7-ol	
-	aniline	
-	2-aminobiphenyl	
-	4-aminobiphenyl	
n-hydroxydiphenylamine	-	
hydroxy hydroquinone of diphenylamine Hydroxy hydroquinone of diphenylamine Quinone of hydroxy diphenylamine	*N*-hydroxy-6-oxo-*N*-phenylcyclohexa-2,4-dien-1-iminium	
O-glucose ester conjugate of diphenylamine	-	

Hydroquinone of diphenylamine	*N*-methyl-*N*-(4-oxocyclohexa-2,5-dien-1-ylidene)anilinium	
Metabolite A glucuronic acid conjugate of 4-hydroxy diphenylamine	-	
Metabolite B sulfate conjugate of 4-hydroxy diphenylamine	-	
2-hydroxy diphenylamine	2-(phenylamino)phenol	
4,4'-dihydroxy diphenylamine	4-[(4-hydroxyphenyl)amino]benzene-1,3-diol	

* The metabolite name in bold is the name used in the conclusion.

ABBREVIATIONS

1/n	slope of Freundlich isotherm
ε	decadic molar extinction coefficient
°C	degree Celsius (centigrade)
µg	microgram
µm	micrometer (micron)
a.s.	active substance
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AV	avoidance factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstract Service
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CIPAC	Collaborative International Pesticide Analytical Council Limited
CL	confidence limits
d	day
DAA	days after application
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
DNA	deoxyribonucleic acid
DPA	diphenylamine
DT_{50}	period required for 50 percent disappearance (define method of estimation)
DT_{90}	period required for 90 percent disappearance (define method of estimation)
dw	dry weight
EbC_{50}	effective concentration (biomass)
EC	emulsifiable concentrate
EC_{50}	effective concentration
ECHA	European Chemical Agency
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
F_1	filial generation, first
F_2	filial generation, second
f(twa)	time weighted average factor
FAO	Food and Agriculture Organisation of the United Nations
FIR	Food intake rate
FOB	functional observation battery

FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
g	gram
GAP	good agricultural practice
GC	gas chromatography
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GGT	gamma glutamyl transferase
GM	geometric mean
GS	growth stage
GSH	glutathion
h	hour(s)
ha	hectare
Hb	haemoglobin
Hct	haematocrit
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HQ	hazard quotient
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
kg	kilogram
K_{Foc}	Freundlich organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
m	metre
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
mL	millilitre
mm	millimetre
MRL	maximum residue limit or level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water holding capacity
NESTI	national estimated short-term intake
ng	nanogram
NOAEC	no observed adverse effect concentration

NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in ground water
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIE	potential inhalation exposure
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r^2	coefficient of determination
RPE	respiratory protective equipment
RUD	residue per unit dose
SC	suspension concentrate
SD	standard deviation
SFO	single first-order
SSD	species sensitivity distribution
STMR	supervised trials median residue
$t_{1/2}$	half-life (define method of estimation)
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TK	technical concentrate
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UV	ultraviolet
W/S	water/sediment
w/v	weight per volume
w/w	weight per weight
WBC	white blood cell
WG	water dispersible granule
WHO	World Health Organisation
wk	week
yr	year