CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion regarding the peer review of the pesticide risk assessment of the active substance diphenylamine

Issued on 30 September 2008

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[1]. This Regulation requires the European Food Safety Authority (EFSA) upon request of the EU 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 EU-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 as laid down in this report.

This conclusion 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. Full details of the GAP can be found in the attached list of endpoints.

[1] 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)

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. 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. The residue meeting of experts has concluded that it might be necessary to set MRLs for products of animal origin. Therefore a data gap is identified for a method of analysis for products of animal origin. If no MRLs are set then of course this data gap will be obsolete.
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. There are several outstanding issues with the technical specification and some aspects of the storage stability and properties of the plant protection product.

In the mammalian metabolism studies, diphenylamine was rapidly and completely absorbed after oral administration, it suffered extensive metabolism to sulphonyl and glucuronyl conjugates and is rapidly excreted mainly via urine. Acute oral and dermal toxicity were low; no acute inhalation toxicity study was submitted, therefore a data gap was set for this study. 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 is 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 only if operators wear gloves. Considering the very specific use of diphenylamine, bystander and worker exposure were not considered relevant.

Metabolism of diphenylamine was investigated in apples having received a post-harvest treatment. Total residues declined only slowly over storage time. Upon analysis diphenylamine was always the major residue, however identification of metabolites was considered insufficient by the meeting of experts and therefore further investigation is required. Also the potential for presence or formation of nitrosamine in apple metabolism or during processing should be addressed by further data, as well as the nature of residues in processed apple commodities. Thus, a plant residue definition for risk assessment and monitoring could only provisionally be proposed.
Livestock metabolism and feeding studies in ruminants were submitted and evaluated. However, the assessment of the nature and magnitude of residues in livestock could not be finalised since different points remained open for further clarification or revision. The applicant made a case that treated apples are destined only for direct human consumption and will not be part of livestock diet. Therefore taking into account livestock exposure and residues in food of animal origin would not be necessary, if it can definitely be excluded that treated apples may become part of livestock diet. Consideration of the issue by risk managers is required. If however there may be dietary exposure of livestock to treated apple commodities, the process of the assessment of nature and magnitude of residues in livestock has to be resumed and continued, and MRLs for food of animal origin will be necessary.
A consumer risk assessment was provisionally performed, assuming the relevant residue was diphenylamine alone and residues were present in apples at the level of the proposed MRL, and in a refined assessment (NEDI) at the level of the median residue found from five available residue trials. While the NEDI was below the ADI for all considered consumer groups, the theoretical maximum daily intake (TMDI) exceeded the ADI for children in one member state diet.

The only data available in the dossier provided, 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.

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BACKGROUND

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. 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, 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 notifier as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the notifier, 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 as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Protection Products and their Residues (PPR).

In accordance with Article 11c(1) of the amended Regulation (EC) No 1490/2002, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received,
- the resulting reporting table (rev 1-1 of 28 February 2008)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation,
- the evaluation table (rev 2-1 of 23 September 2008).

Given the importance of the draft assessment report including its addendum (compiled version of July 2008 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

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 attached list of endpoints.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

At the moment no minimum purity of diphenylamine as manufactured can be given, because further clarification is needed. The current specification relies on a method that is not validated for the active substance in the technical material. In addition to this a full specification of the starting material is missing.

Since the minimum purity of the active substance can not be agreed the specification as a whole remains provisional.

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).

Besides the specification and the fact that it was confirmed by the applicant that certain tank mixes may result in the formation of nitrosamines, the assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of diphenylamine or the respective formulations. However, the following data gaps were identified:

- Spectra for the relevant impurities.
- Evidence to demonstrate that when opened containers are stored diphenylamine remains stable.
- Emulsion stability at the minimum in use concentration.

The main data regarding the identity of diphenylamine and its physical and chemical properties are given in appendix 1.

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[2] isomers in surface water. A method is not available for products of animal origin and as MRLs may be set a data gap has been identified. If MRLs for products of animal origin are not set then this data gap will be obsolete.

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

Residues in apples are analysed using the German S19, 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 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 was available for the analysis of human plasma with a LOQ of 0.05 mg/L but this is not required because the active substance is neither toxic nor very toxic.

2. Mammalian toxicology

Diphenylamine was discussed at the PRAPeR Expert's Meeting on mammalian toxicology (PRAPeR 49) in June 2008.

No analysis of the impurity profile of the batches used in the toxicological studies is available. The meeting agreed to set a data gap for this information.
The meeting agreed also 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, no concern is raised.

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. No acute inhalation toxicity study was available, this study should be submitted and a data gap was set. 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 from 96 mg/kg bw/day on.

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 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 several 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. Again 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; none is required.

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, 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 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 meeting 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[3]. The experts noted that this value is most likely unrealistic; it is up to the Member States to require a study.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

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

Diphenylamine is used post-harvest in indoor drench tanks on apples and pears 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 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: gloves

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; worker exposure was not considered relevant.

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] Sanco/222/2000 rev.6 of November 27, 2002 – Guidance Document on Dermal Absorption

3. Residues

Diphenylamine was discussed in the meeting of experts in Residues PRAPeR 50 in June 2008 (Round 10) on the basis of Vol. 3 B.7 of the draft assessment report and the addendum of April 2008. Additional information provided after the meeting of experts in the addendum of July 2008, was not peer reviewed by Member States and EFSA and is therefore not taken into account in the EFSA conclusion.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

The metabolism was studied with [^{14}C] ring labelled diphenylamine in post harvest treated apples. Upon application (12.5 N rate) the apples were kept in cold storage. On the day of application and at intervals of 12, 24 and 40 weeks after application samples of fruit were taken for analysis.

The amount of total radioactive residues found in the whole apple remained relatively constant within 24 weeks after treatment (day 0: 55 mg/kg; 24 weeks: 50 mg/kg), but had decreased after 40 weeks (37 mg/kg). Over the course of the study there was penetration of radioactive residues from the surface into apple pulp, and hence pulp residues steadily increased within 40 weeks of storage 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).

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 residue (100% of TRR) present in treated apples. After that period levels of diphenylamine showed a consistent decline to 54% of TRR (20 mg/kg) at 40 weeks of storage. An analysis of metabolites by LC-MS identified the hydroquinone of diphenylamine (2.3- 4.9% TRR, up to 1.8 mg/kg), the O-glucose ester conjugate of diphenylamine (3.7- 7% TRR, up to 3.3 mg/kg), n-hydroxydiphenylamine and the quinone of hydroxy-diphenylamine (0.4 -7.9% TRR, up to 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. Component 3 was also found in samples taken at 12 weeks interval. All three unknown metabolite fractions are expected to be present at levels greater than 0.05 mg/kg when apples are treated at N rate. Therefore, the meeting of experts agreed that the identity of metabolites present in significant amounts in treated apples should be clarified (data gap).

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 on 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 on the possible formation of nitrosamines in case of tank mixing, the applicant was asked to address whether there could be a probability of formation of nitrosamines in metabolism or under processing. The meeting couldn't 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. Therefore a data gap has been proposed for the applicant to investigate the potential presence of nitrosamines. The data gap is linked to the data gaps regarding further clarification of identity of metabolites in apple and the nature of the residues in apple processed commodities.

Currently, the residue definition for risk assessment and monitoring purposes is provisionally proposed as diphenylamine. A final residue definition is pending the submission of data addressing the identified data gaps with regard to metabolites, breakdown and reaction products including nitrosamines. The applicability of the proposed residue definition to crops or commodities other than in the category of the evaluated use in post harvest treated apples has not been assessed.

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 at the maximum notified use rate were quantified. The treated apples were stored in controlled atmosphere for up to 260 days (37 weeks) and samples were taken for analysis at different intervals following application.
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 this set of 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 while in the second trial residues in the whole apple were only determined at the day of treatment (day 0).
From the total of trials the critical residue values for diphenylamine in apple ranged between 1.2 and 3.4 mg/kg. After extensive discussion on whether or not the available data show the level of homogeneity expected for post-harvest treated crops, as set out in the guidance document[4], 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 show

[4] Guidance document SANCO 7525/VI/95 rev. 8: Guidelines on comparability, extrapolation, group tolerances and data requirements

higher residues than in trials with drench application, but their assessment has been outside the scope of the remit of the peer review.

Submitted data on freezer storage stability indicated residues of diphenylamine can be considered as being stable in whole apples and processed apple fractions (juice and pomace). All results in the residue studies were generated with validated analytical methods.

No study was provided that investigated 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.). As required by directive 91/414/EEC, this case has to be addressed, and therefore the experts agreed that investigations as set out in the guidance document[5] should be performed. A new data gap for data on the nature of the residues in apple processed commodities has been identified.

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 factors for apple juice, 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 the dry pomace than in the wet pomace due to concentration by the loss of water, unless there was degradation of diphenylamine during the drying process. A new data gap was identified regarding further clarification on the results from the processing studies, i.e. to confirm the residue levels determined for wet and dry pomace.

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 to determine the manner in which diphenylamine is metabolised in these animals. Diphenylamine is considered a fat-soluble compound and may therefore accumulate in body tissue.

As for the use on apples, the only relevant feed item would be apple pomace. Since fruit pomace is usually not fed to chicken, the study with laying hens is not a requirement to support the current

[5] Guidance document SANCO/7035/VI/95 rev.5 on processing studies

notification for diphenylamine. Therefore, the study is not further considered here in this document, but a summary has been made available in the DAR for future reference.

As for ruminants, the notifier argued 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 animals. 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. 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 residues in animal matrices could be expected and MRLs would have to be proposed. To decide if this evaluation will be relevant for the notified use, risk managers should consider whether or not livestock exposure can indeed be excluded or avoided. It is noted that information provided by the RMS in the addendum of July 2008 is not peer reviewed by Member States and EFSA.

The meeting of experts addressed livestock exposure only from a scientific point of view. The experts considered the available livestock metabolism studies as valid and acceptable, but noted the need for clarification on the feeding rate in the study with regard to the dry matter (DM) intakes.
In the goat study diphenylamine was identified as the major residue in kidney (36% TRR) and omental fat (36% TRR), and was also present in milk (7.4% TRR) and liver (5.9% TRR). In addition, in milk, kidney and liver 86 %, 38% and 11% of the TRR, respectively, were identified as the glucuronic acid and sulphate conjugates of 4-hydroxy diphenylamine.
As being the predominant residue in milk these conjugates should be included in addition to diphenylamine in the residue definition for risk assessment if they were considered of toxicological significance. For monitoring purposes the residue definition for food of animal origin was proposed as diphenylamine alone. It is noted that the proposed residue definitions are provisional.
The need to continue the assessment and/or to require further data is pending clarification with respect to the potential for livestock exposure from the notified use in apples. As already highlighted above, consideration of the issue by risk managers will be required.

A feeding study with 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. The analytical method was fully validated to determine diphenylamine with a LOQ of 0.005 mg/kg. Residues above LOQ were detected in milk, liver and fat samples from all 3 dose groups, and in kidney samples from the highest dose group. No diphenylamine was found above LOQ in muscle samples.
According to the livestock dietary burden calculation presented in the addendum of April 2008 the medium and highest dose group would be appropriate to estimate potential residue levels in products

from dairy and beef cattle respectively. In case ruminants are exposed to diphenylamine residues through diet, transfer of these residues into animal tissue is expected at levels of 0.006 mg/kg in whole milk, 0.11 mg/kg in fat, 0.26 mg/kg in liver and 0.01 mg/kg in kidney. The determined residue levels indicate the MRLs would have to be set. With regard to the inconsistency in the residue levels of apple pomace (see 3.1.1 above), the meeting noted the need to review the livestock dietary intake assessment and if necessary to adapt the MRL proposals for livestock matrices accordingly.

Currently it is not possible to conclude this area of assessment. Further consideration with regard to livestock exposure to diphenylamine residues in relation to the notified use is necessary to proceed with the issue. If it turned out that it cannot be excluded that treated apples may become part of livestock diet, the process of the evaluation of nature and magnitude of residues in livestock has to be resumed and continued, and reviewed MRL proposals for livestock matrices are required.

3.3. CONSUMER RISK ASSESSMENT

The meeting of experts considered dietary intake estimates submitted by the RMS in the addendum of April 2008. The RMS used consumption data in the EFSA PRAPeR model. Residues of diphenylamine were assumed to be present in all apples including apples destined for processing at the level of the proposed MRL of 10 mg/kg, and in meat and milk at a level of 0.01 mg/kg. With the previously proposed ADI of 0.03 mg/kg bw/day the TMDI was shown to exceed the ADI, in particular for the consumer sub-group of children (400 % of the ADI for a German child, about 200 % for a Dutch child and 100% for a Danish child) The major contributor was apples; consideration of animal products in the intake estimates leads only to an insignificant increase by 1% or less of the ADI.
A refined dietary intake estimate (NEDI) with the median residue (STMR) seen in residue trials showed that residue exposure from apples alone nearly reached 100% of the ADI for children. The meeting of experts discussed uncertainty concerning the result with regard to the STMR used in the assessment, considering the limited number of residue values available to determine the STMR.

After the meeting of experts on residues had finalised the discussion on diphenylamine, the meeting on toxicology agreed a new (higher) ADI of 0.075 mg/kg bw/ day. In the addendum of July 2008 (not peer reviewed) the RMS revised the consumer intake and risk assessment to take into account the changes agreed in PRAPeR 49 and 50. With the new ADI the maximum estimated daily intake (TMDI) using the proposed MRL of 10 mg/kg is about 160% of the ADI for a German child and 85% for a Dutch child. Other consumer groups in the model had much lower exposure. The refined assessment (NEDI) using the new STMR of 2.39 mg/kg demonstrated that the intakes for all considered consumer groups were well below (>40%) the new ADI of 0.075 mg/kg bw/ day. Contribution from residues in food of animal origin to consumer exposure was in all cases negligible (<1% ADI).

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

3.4. PROPOSED MRLS

For the representative use on apples treated with diphenylamine by drench application, a MRL of 10 mg/kg is proposed. The MRL is provisional, pending confirmation of the residue definition for monitoring (see chapter 3.1.1 above).
It is noted that, when using a possible maximum residue level of 10 mg/kg in apples in the chronic dietary intake assessment, the ADI was shown to be exceeded for the vulnerable consumer group of children (German child).

Provisionally proposed MRLs for food of animal origin, pending further clarification and review (see chapter 3.2 above):

Liver	0.3 mg/kg
Meat on a fat basis	0.1 mg/kg
Kidney	0.01 mg/kg
Milk (whole product)	0.01 mg/kg

It is noted that no validated methods for monitoring residues in food of animal origin have been submitted. Therefore the LOQ of a potential method is not known.
Information submitted by the RMS in the addendum of July 2008 was not peer reviewed by Member States and EFSA and was therefore not considered.

4. Environmental fate and behaviour

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 dependant 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[6], D2[7] and D3 isomers I[8] and II[9]) 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.

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

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

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.

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 applied for intended use was 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 IIl

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 apples have been fully identified. (for details refer to chapter 3.1.1 of this document)
Definition for monitoring: diphenylamine, provisional until metabolites / degradation products in apples have been fully identified. (for details refer to chapter 3.1.1 of this document)

Food of animal origin

Definition for risk assessment: not finalised (for details refer to chapter 3.2 of this document)
Definition for monitoring: diphenylamine, provisional (for details refer to chapter 3.2 of this document)

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
None, but diphenylamine if there is misuse	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.

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 if there is misuse	No data available	No	Diphenylamine yes	Diphenylamine yes	Diphenylamine yes

Surface water and sediment

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

Air

Compound (name and/or code)	Toxicology
diphenylamine	No data – data required

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- A detailed specification of the starting material has been identified as a data gap (relevant for all uses, data gap identified by meeting of experts May 2008, date of submission unknown, refer to chapter 1)
- A new specification is required with the correct minimum purity and the relevant impurities (relevant for all uses, data gap identified by meeting of experts May 2008, date of submission unknown, refer to chapter 1)
- Spectra for the relevant impurities (relevant for all uses, data gap identified by meeting of experts May 2008, date of submission unknown, refer to chapter 1)
- Evidence to demonstrate that when opened containers are stored diphenylamine remains stable (relevant for all uses, data gap identified by meeting of experts May 2008, date of submission unknown, refer to chapter 1)
- Emulsion stability at the minimum in use concentration (relevant for all uses, data gap identified by meeting of experts May 2008, date of submission unknown, refer to chapter 1)
- Method of analysis for D3 in surface water (relevant for all uses, data gap identified by EFSA September 2008, date of submission unknown, refer to chapter 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 chapter 1)
- Information on the impurity profile of the batches used in key toxicological studies (relevant for all representative uses evaluated; no submission date proposed by the notifier; refer to point 2)
- An acute inhalation toxicity study conducted with diphenylamine (relevant for all representative uses evaluated; no submission date proposed by the notifier; refer to point 2.2)
- The identity of metabolites present in significant amounts in treated apples should be clarified (relevant for all representative uses evaluated; data gap identified by meeting of experts in June 2008; RMS advised information is available; refer to chapter 3.1.1)
- The applicant should investigate the potential presence of nitrosamines in metabolism or under processing (relevant for all representative uses evaluated; data gap identified by meeting of experts in June 2008; RMS advised information is available; refer to chapter 3.1.1)
- A study investigating the nature of the residues in apple processed commodities (relevant for all representative uses evaluated; data gap identified by meeting of experts in June 2008; no submission date proposed by the notifier; refer to chapter 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 all representative uses evaluated; data gap identified by meeting of experts June 2008; RMS advised information is available; refer to chapter 3.2)
- Clarification on the feeding rate in the livestock studies with ruminants with regard to the dry matter (DM) is required (relevant for all representative uses evaluated; data gap identified by meeting of experts June 2008; RMS advised information is available; refer to chapter 3.2)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

This conclusion 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. Full details of the GAP can be found in the attached list of endpoints.

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. 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. The residue meeting of experts has concluded that it might be necessary to set MRLs for products of animal origin. Therefore a data gap is identified for a method of analysis for products of animal origin. If no MRLs are set then of course this data gap will be obsolete.

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. There are several outstanding issues with the technical specification and some aspects of the storage stability and properties of the plant protection product.

In the mammalian metabolism studies, diphenylamine was rapidly and completely absorbed after oral administration, it suffered extensive metabolism to sulphonyl and glucuronyl conjugates and is rapidly excreted mainly via urine. Acute oral and dermal toxicity were low; no acute inhalation toxicity study was submitted, therefore a data gap was set for this study. 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 is 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 evidence 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 only if operators wear gloves. Considering the very specific use of diphenylamine, bystander and worker exposure were not considered relevant.

Metabolism of diphenylamine was investigated in apples having received a post-harvest treatment. Total residues declined only slowly over storage time. Upon analysis diphenylamine was always the major residue, however identification of metabolites was considered insufficient by the meeting of experts and therefore further investigation is required. Also the potential for presence or formation of nitrosamine in apple metabolism or during processing should be addressed by further data, as well as the nature of residues in processed apple commodities. Thus, a plant residue definition for risk assessment and monitoring could only provisionally be proposed.
Livestock metabolism and feeding studies in ruminants were submitted and evaluated. However, the assessment of the nature and magnitude of residues in livestock could not be finalised since different points remained open for further clarification or revision. The applicant made a case that treated apples are destined only for direct human consumption and will not be part of livestock diet. Therefore taking into account livestock exposure and residues in food of animal origin would not be necessary, if it can definitely be excluded that treated apples may become part of livestock diet. Consideration of the issue by risk managers is required. If however there may be dietary exposure of livestock to treated apple commodities, the process of the assessment of nature and magnitude of residues in livestock has to be resumed and continued, and MRLs for food of animal origin will be necessary.
A consumer risk assessment was provisionally performed, assuming the relevant residue was diphenylamine alone and residues were present in apples at the level of the proposed MRL, and in a refined assessment (NEDI) at the level of the median residue found from five available residue trials. While the NEDI was below the ADI for all considered consumer groups, the theoretical maximum daily intake (TMDI) exceeded the ADI for children in one member state diet.

The only data available in the dossier provided, 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.

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

- Operator exposure was estimated to be below the AOEL only if gloves were worn, according to the mixing and loading phase of the German model (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.

Critical areas of concern

- The specification can not be finalised.
- Some tank mixes may result in the formation of nitrosamines therefore these should be carefully assessed on a case by case basis.

- Finalisation of the consumer risk assessment is pending the submission of data addressing the identified data gaps on identity of metabolites, on potential occurrence of nitrosamines and degradation products under processing conditions in apple commodities. It is also open whether in practice there can be consumer exposure from food of animal origin and whether MRL setting for animal commodities is needed.
- In a provisional estimate of the theoretical maximum daily intake, using the proposed MRL for diphenylamine in apples, the ADI was exceeded in one Member States diet.

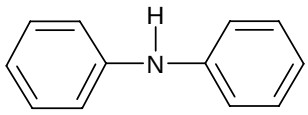
Appendix 1 – list of endpoints

APPENDIX 1 – LIST OF ENDPOINTS 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 ‡	OPEN
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 ‡	

Appendix 1 – list of endpoints

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).

Appendix 1 – list of endpoints

UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	λmax was determined at 284 nm with a second band at 204 nm. At 284 nm the log10 ε was 4.32 (methanol), 4.57 (acidified methanol) and 4.37 (basic methanol). At 204 nm the log10 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%).

Appendix 1 – list of endpoints

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	[1] [2]

[1] There are data gaps in section 1
[2] Consumer risk assessment is not finalised due to data gaps identified in section 3 (Residues).

*	For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier 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

Appendix 1 – list of endpoints

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 animal origin (analytical technique and LOQ for methods for monitoring purposes)	Open data gap if MRLs are not set this data gap will be obsolete.
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 Not required [substance is not classified as toxic (T) or very toxic (T$^+$)]

Appendix 1 – list of endpoints

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)	Parent compound
Toxicologically relevant compounds ‡ (environment)	Parent compound

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	> 15000 mg/kg bw	
Rabbit LD_{50} dermal ‡	> 7500 mg/kg bw	
Rat LC_{50} inhalation ‡	No data, study required	
Skin irritation ‡	Not irritant	
Eye irritation ‡	Severe irritant	**R41**
Skin sensitisation ‡	Non-sensitiser (Magnusson & Kligman)	

Appendix 1 – list of endpoints

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	

Appendix 1 – list of endpoints

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 - not required

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	-	-

Appendix 1 – list of endpoints

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
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"

Appendix 1 – list of endpoints

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
Rotational crops	Not relevant for post harvest use.
Metabolism in rotational crops similar to metabolism in primary crops?	Not relevant.
Processed commodities	**No data submitted** - data gap identified for a study on the nature of the residue in processed commodities
Residue pattern in processed commodities similar to residue pattern in raw commodities?	**Open** (data gap identified -see above)
Plant residue definition for monitoring	Diphenylamine - **provisional** until the metabolites in apples and potential degradation products under processing have been fully identified.
Plant residue definition for risk assessment	Diphenylamine - **provisional** until the metabolites in apples and potential degradation products under processing have been fully identified.
Conversion factor (monitoring to risk assessment)	**Open** - Pending finalisation of residue definitions

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

Animals covered	Goat
Time needed to reach a plateau concentration in milk and eggs	Not reported
Animal residue definition for monitoring	Diphenylamine – **provisional**
Animal residue definition for risk assessment	**Not finalised** – pending further assessment on metabolites
Conversion factor (monitoring to risk assessment)	**Open** -Pending finalisation of animal residue definitions
Metabolism in rat and ruminant similar (yes/no)	Yes. No necessity for a metabolism study with pigs.
Fat soluble residue: (yes/no)	Yes (log $P_{O/W}$ > 3). Measurable residues of DPA were observed in fat in a dairy cow study.

Appendix 1 – list of endpoints

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)

The study shows that diphenylamine residues in apples and in processed apple matrices showed no significant decreases when stored in a freezer for time periods between 155 and 202 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[j] Dairy cattle: 6 mg/kg feed DM (120 mg/cow/day) Beef cattle: 18 mg/kg feed DM (270 mg/cow/day)	[1]No	[1]No
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 [a]	n/a	n/a
	Feeding studies: 90 mg [group 3] and 300 mg [group 4] of diphenylamine/cow/day (intake in mg/kg feed on dry weight basis not available– data gap) Residue levels in matrices: Mean (max) mg/kg		
Muscle	<0.005 (<0.005) [groups 3 & 4]	n/a	n/a
Liver	0.053 (0.070) [group 3] 0.153 (0.257) [group 4]	n/a	n/a

[j] The assessment was based on the worst -case assumption that treated apples could be part of livestock diet.

Appendix 1 – list of endpoints

Kidney	<0.005 (<0.005) [group 3] 0.007 (0.010) [group 4]	n/a	n/a
Fat	0.018 (0.020) [group 3] 0.053 (0.109) [group 4]	n/a	n/a
Milk	<0.005 (0.006) [group 3] 0.006 (0.014) [group 3]		
Eggs		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.

Appendix 1 – list of endpoints

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 (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.	1.19, 1.32, 2.39, 2.44 and 3.37 mg/kg	**Drench application:** There are 5 different apple trials, which support the supplied GAP. According to provisionally proposed residue definition.	MRL = 10 mg/kg (for drench application)	3.37	2.39

(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

Appendix 1 – list of endpoints

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

ADI	0.075 mg/kg bw/day
TMDI (% ADI) according to WHO European diet	**provisional**-pending finalisation of residue definition for risk assessment 12.8% (0.009583 mg/kg bw/day)
TMDI (% ADI) according to national diets	**provisional**-pending finalisation of residue definition for risk assessment German 2-5 yr old child (16.15 kg bw): 160.9% (0.1207 mg/kg bw/day, based on total apple consumption), additional exposure from food of animal origin <1%.
IEDI (WHO European Diet) (% ADI)	Not assessed.
NEDI (% ADI)	No peer reviewed assessment available.[11]
Factors included in IEDI and EDI	Not applicable.
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).

[11] revised intake calculation submitted by RMS in the non peer reviewed addendum of July 2008; with the EFSA PRAPeR model, when the STMR for apples and the proposed MRLs for food of animal origin used, highest intake was less than 40% ADI for German children; assessment **provisional** pending finalisation of the residue definition for risk assessment

Appendix 1 – list of endpoints

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor [8]	Yield factor [8]	
State combination of crop, process and processed product for which results are available. If more than one product is obtained in a single process, take a line for every processed product. (see also Guidance Document Appendix E)	Indicate number of studies available for the specified combination.	Average factor from the results of the different studies for the specified combination. Individual results to be mentioned in brackets		
Apple juice	1	0.048 (0.047, 0.039, 0.023, 0.082)	[8,9]	[8]
Wet Pomace	1	4.375 (4.86, 3.30, 3.31, 6.03)		
Dried Pomace	1	2.28 [12] (1.85, 1.90, 2.42, 2.95)		

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

Food of plant origin:

Proposed MRLs	10 mg/kg in apples (for drench application) **provisionally proposed-** pending confirmation of monitoring residue definition

[12] factor is subject to clarification on why residues in wet pomace where higher than in dried pomace, usually concentration of residues upon drying results in a higher transfer factor for dried pomace than for wet pomace (data gap)

Appendix 1 – list of endpoints

Food of animal origin:

Proposed MRLs*	Diphenylamine is considered fat soluble. The experts in PRAPeR 50 agreed that MRL proposals for food of animal origin are required if it can not definitely be excluded that residues of diphenylamine could get into animal diet. Further consideration by risk managers is required. **Provisionally proposed MRLs** pending review: Milk (whole product basis) 0.01 mg/kg Meat (on fat basis) 0.1 mg/kg [Note that residues in whole meat were <0.005 mg/kg] Liver (on whole product basis) 0.3 mg/kg Kidney (on whole product basis) 0.01 mg/kg

Appendix 1 – list of endpoints

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

Appendix 1 – list of endpoints

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

Appendix 1 – list of endpoints

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 ☒ > 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

Appendix 1 – list of endpoints

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 ☒ > 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 x 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 x 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 metabolite 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

Appendix 1 – list of endpoints

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 ‡				

Appendix 1 – list of endpoints

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
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				

Appendix 1 – list of endpoints

[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

Appendix 1 – list of endpoints

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 2 – ABBREVIATIONS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
a.s.	active substance
AV	avoidance factor
BCF	bioconcentration factor
bp	boiling point
bw	body weight
c	centi- (x 10^{-2})
°C	degree Celsius (centigrade)
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
cm	centimetre
d	day
DAR	draft assessment report
DM	dry matter
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days past inoculation
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
ECD	electron capture detector
ED_{50}	median effective dose
EDI	estimated daily intake
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
F	field

Appendix 2 – abbreviations

F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FPD	flame photometric detector
f(twa)	time weighted average factor
g	gram
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GLC	gas liquid chromatography
GLP	good laboratory practice
GS	growth stage
h	hour(s)
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
IEDI	international estimated daily intake
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
inh	inhalation
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H)13
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
kg	kilogram
L	litre

Appendix 2 – abbreviations

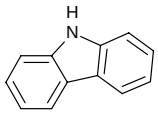
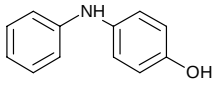
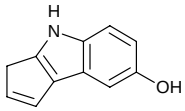
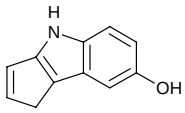
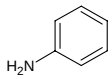
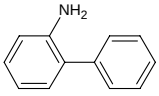
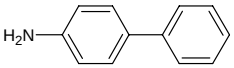
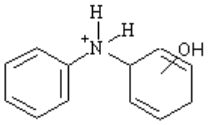
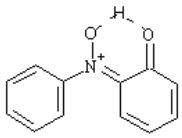
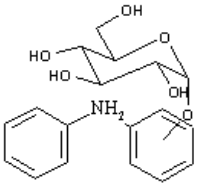
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
m	metre
M	molar
MAF	multiple application factor
µm	micrometer (micron)
MC	moisture content
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
mm	millimetre
mN	milli-Newton
mo	month(s)
mol	Mol
MOS	margin of safety
mp	melting point
MRL	maximum residue limit or level
MS	mass spectrometry
MSDS	material safety data sheet
n	normal (defining isomeric configuration)
NAEL	no adverse effect level
nd	not detected
NEDI	no effect daily intake (mg/kg body wt/day)
NESTI	national estimated short term intake
ng	nanogram
NIR	near-infrared-(spectroscopy)
nm	nanometer
NMR	nuclear magnetic resonance
no	number

Appendix 2 – abbreviations

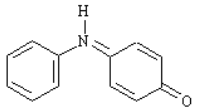
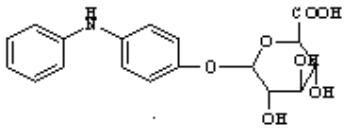
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen-phosphorus detector or detection
OC	organic carbon content
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
pH	pH-value
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
s	second
STMR	supervised trials median residue
TC	technical material
TER	toxicity exposure ratio
TK	technical concentrate
TMDI	theoretical maximum daily intake
TRR	total radioactive residues
TWA	time weighted average
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

Appendix 3 – used compound code(s)

APPENDIX 3 – 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	?-(phenylamino)phenol	
n-hydroxy hydroquinone of diphenylamine		
o-glucose ester conjugate of diphenylamine		

Appendix 3 – used compound code(s)

Code/Trivial name	Chemical name	Structural formula
Hydroquinone of diphenylamine		
Metabolite A, glucuronic acid conjugate of 4- hydroxy diphenylamine		
Metabolite B, sulfate conjugate of 4- hydroxy diphenylamine