CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion on the peer review of the pesticide risk assessment of confirmatory data submitted for the active substance diflubenzuron[1]

European Food Safety Authority[2]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessment carried out by the competent authority of the rapporteur Member State Sweden, for the pesticide active substance diflubenzuron are reported. The context of the peer review was that requested by the European Commission following the submission and evaluation of confirmatory mammalian toxicology data. The conclusions were reached on the basis of the evaluation of the representative uses of diflubenzuron as an insecticide on apples, pears and mushrooms, and in forestry. The reliable endpoints concluded as being appropriate for use in regulatory risk assessment, derived from the available studies and literature in the dossier peer reviewed, are presented. Concerns are identified.

KEY WORDS

Diflubenzuron, peer review, risk assessment, pesticide, insecticide

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SUMMARY

Diflubenzuron was included in Annex I to Directive 91/414/EEC on 1 January 2009 by Commission Directive 2008/69/EC (amended by Commission Directive 2010/39/EU), and has been deemed to be approved under Regulation (EC) No 1107/2009, in accordance with Commission Implementing Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011. It was a specific provision of the approval that the notifier was required to submit to the European Commission further studies on the potential genotoxicity of the impurity and metabolite 4-chloroaniline (PCA) by 30 June 2011.

In accordance with the specific provision, the notifier, Chemtura Netherlands B.V, submitted an updated dossier in June 2011, which was evaluated by the designated RMS, Sweden, in the form of an Addendum to the Draft Assessment Report. In compliance with Guidance Document SANCO 5634/2009 rev.3, the RMS distributed the Addendum to Member States and the EFSA for comments on 20 December 2011. The RMS collated all comments in the format of a Reporting Table, which was submitted to the European Commission in April 2012.

Following consideration of the comments received, the European Commission requested the EFSA to organise a peer review of the RMS's evaluation of the confirmatory data submitted in relation to the potential toxicological relevance of the impurity and metabolite 4-chloroaniline (PCA) and to deliver its conclusions on the risk from exposure to PCA via intake of or exposure to diflubenzuron for consumers, residents/bystanders and workers.

The experts at the Pesticides Peer Review Meeting on mammalian toxicology (PPR 92) in July 2012 concluded that PCA as a metabolite in both humans and rats should be considered as a transient non-isolatable metabolite after exposure to diflubenzuron. The rat should be considered an appropriate model for human exposure to diflubenzuron where a genotoxic and carcinogenic potential was not observed. However, it is noted that the concentration of the carcinogenic impurity PCA in the batches tested in the carcinogenicity studies is still unknown. The EFSA in 2009 identified a critical area of concern concerning the lack of a peer reviewed specification and assessment of the equivalence of the batches tested in all the mammalian toxicity studies compared to the representative specification. The EFSA considered it particularly important because of the unknown concentration of the PCA in the batches tested in the carcinogenicity studies. The experts considered that potential exposure to PCA as a residue (i.e. either for consumers or for workers and bystanders/residents) should be considered *a priori* as a concern since a threshold for a genotoxic carcinogen cannot be assumed.

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BACKGROUND

Diflubenzuron was included in Annex I to Directive 91/414/EEC on 1 January 2009 by Commission Directive 2008/69/EC[3] (amended by Commission Directive 2010/39/EU[4]), and has been deemed to be approved under Regulation (EC) No 1107/2009[5], in accordance with Commission Implementing Regulation (EU) No 540/2011[6], as amended by Commission Implementing Regulation (EU) No 541/2011[7]. EFSA previously finalised a Conclusion on this active substance on 16 July 2009 in the EFSA Scientific Report (2009) 332 (EFSA, 2009).

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The Addendum and the Reporting Table were discussed at the Pesticides Peer Review Meeting on mammalian toxicology (PPR 92) in July 2012. Details of the issues discussed, together with the outcome of these discussions were recorded in the meeting report.

A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in July - August 2012.

The conclusions laid down in this report were reached on the basis of the peer review of the RMS's evaluation of the confirmatory data submitted in relation to the potential toxicological relevance of the impurity and metabolite PCA. A key supporting document to this conclusion is the Peer Review Report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the compilation of comments in the Reporting Table to the conclusion.

[3] Commission Directive 2008/69/EC of 1 July 2008 amending Council Directive 91/414/EEC to include clofentezine, dicamba, difenoconazole, diflubenzuron, imazaquin, lenacil, oxadiazon, picloram and pyriproxyfen as active substances. OJ No L 172, 2.7.2008, p. 9-14.

[4] Commission Directive 2010/39/EU of 22 June 2010 amending Annex I Council Directive 91/414/EEC as regards the specific provisions relating to the active substances clofentezine, diflubenzuron, lenacil, oxadiazon, picloram and pyriproxyfen as active substances. OJ No L 156, 23.6.2010, p. 7-11.

[5] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ No L 309, 24.11.2009, p. 1-50.

[6] Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p.1-186.

[7] Commission Implementing Regulation (EU) No 541/2011 of 1 June 2011 amending Implementing Regulation (EU) No 540/2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p.187-188.

The Peer Review Report (EFSA, 2012b) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the Reporting Table,
- the report of the scientific consultation with Member State experts,
- the comments received on the draft EFSA conclusion.

Given the importance of the Addendum to the DAR and the Peer Review Report, these documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Diflubenzuron is the ISO common name for 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea (IUPAC).

Diflubenzuron belongs to the class of chitin synthesis inhibitors. It is a non-systemic insect growth regulator with contact and stomach action.

The representative formulated product for the evaluation was 'Dimilin WG 80', a water dispersible granule (WG).

The evaluated representative uses are as an insecticide on apples, pears and mushroom, and in forestry.

CONCLUSIONS OF THE EVALUATION

The notifier submitted to the Commission by the deadline of 30 June 2011 the following studies on the potential genotoxicity of the impurity and metabolite 4-chloroaniline (PCA):

- Repeat micronucleus test in mice
- Rat liver UDS study
- Rat comet assay

Based on genotoxicity studies submitted by the notifier the weight of evidence suggests that PCA is an *in vivo* genotoxic agent. PCA is a carcinogenic agent (Carcinogen Cat 2; R 45, May cause cancer[8]).

Potential exposure to PCA can occur as a metabolite via intake of or exposure to diflubenzuron, or as an impurity present in the technical material or as residue (i.e. direct exposure to PCA).

PCA as a **metabolite** in both humans and rats should be considered as a transient non-isolatable metabolite after exposure to diflubenzuron. Although there are uncertainties on the amount formed in different species the experts agreed that the rat should be considered an appropriate model for human exposure to diflubenzuron where a genotoxic and carcinogenic potential were not observed. However, the concentration of the carcinogenic **impurity** PCA in the batch tested in the carcinogenicity studies is still unknown (i.e. the EFSA considered the retrospective analysis of the batch not reliable). In 2009 the EFSA identified a critical area of concern concerning the lack of a peer reviewed specification and assessment of the equivalence of the batches tested in all the mammalian toxicity studies compared to the representative specification. This was considered particularly important because of the unknown concentration of the PCA in the batches tested in the carcinogenicity studies.

Potential exposure to PCA as a **residue** (i.e. either for consumers or for workers and bystanders/residents) should be considered *a priori* as a concern since a threshold for a genotoxic carcinogen cannot be assumed (i.e. AOEL, ADI and ARfD cannot be set).

During the meeting the applicability of the margin of exposure approach (MoE) (EFSA, 2012a) from a scientific point of view to perform a risk assessment for exposure to PCA as a residue was discussed. It was concluded that, based on current toxicological data, which is not sufficient to set a reference point as the basis for MoE and the lack of exposure estimates in workers and bystanders/residents, the approach cannot be justified from a scientific point of view.

[8] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ No L 353, 31.12.2008. p. 1-1355

In addition, it is considered that a sound consumer exposure assessment for PCA as a residue in food would be indispensible. The currently available residue data are unsuitable to determine the occurrence of PCA in the concerned foods of plant and animal origin at levels that are required for assessing genotoxic carcinogenic compounds, i.e. a LOQ of the analytical method to 0.00001 mg/kg food would be necessary to obtain meaningful data. The requirements for new data on the magnitude of residues in mushrooms and in food of animal origin, including the supporting data for freezer storage stability as set out in the EFSA conclusion of 2009, are still applicable, however the required performance of the analytical method should be taken into account when conducting the studies. In addition, new residue trials in pome fruit determining PCA and possibly CPU with a sufficiently low LOQ would be needed in order to conduct a robust consumer risk assessment, as well as new data for wild berries and mushrooms after application of diflubenzuron in the forest, if the MoE approach were to be applied for consumer risk assessment.

The presence of PCA and its structural precursor CPU in the metabolic pathway in plants has been demonstrated in the metabolism studies in apples and mushrooms at concentration levels that are deemed pertinent for a dietary risk assessment in view of the genotoxic carcinogenic properties of PCA. Since metabolite CPU has no adequate toxicity data, as a precautionary approach it is provisionally included in the residue definition together with PCA, pending the finalisation of the toxicological evaluation of CPU. The plant residue definition for risk assessment provisionally proposed in 2009 should be amended and now defined as follows:

- For fruit crops after foliar application 1) diflubenzuron and 2) Sum of CPU and PCA expressed as PCA.

- For mushrooms after soil application: 1) Sum of diflubenzuron and DFBA expressed as diflubenzuron and 2) Sum of CPU and PCA expressed as PCA.

The animal residue definition for risk assessment is updated as follows, pending the finalisation of the toxicological evaluation of CPU and PCAA:

- 1) Diflubenzuron and 2) Sum of CPU, PCA and PCAA expressed as PCA.

A third party evaluation (JMPR, 2002) contained summaries of hydrolysis studies that are considered relevant in terms of the tested parameters (pH, temperature and time) to address conditions applicable to food processing and storage of processed food commodities. The reported data indicate that diflubenzuron decomposes to form significant amounts of both compounds CPU and PCA. A study on the effect of processing on the nature of residues is required to elaborate the rate and the proportions at which CPU and PCA might be formed in processed food commodities in addition to the amounts already present as metabolites of diflubenzuron. Different from the 2009 EFSA conclusion the required study should cover all three representative conditions to obtain a more complete view of the behaviour of diflubenzuron residues under different hydrolytic conditions. Depending on the results it might be necessary to require additional processing studies in fruits and mushrooms determining residue levels according to the residue definition for risk assessment with an adequately low LOQ.

A reliable assessment of consumer exposure to residues of PCA in food commodities is currently not possible due to the lack of sufficient residue data in food of plant and animal origin.

Concerns

1. Issues that could not be finalised

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

1. Data on potential exposure of workers and bystanders/residents to PCA are missing. Potential exposure to PCA as a residue should be considered as a concern since a threshold for a genotoxic carcinogen cannot be assumed. In case the margin of exposure (MoE) approach were to be applied for worker and resident risk assessment of carcinogenic genotoxic metabolites, toxicological data and exposure estimates are insufficient to perform the MoE assessment.

2. Critical areas of concern

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

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

2. Lack of peer reviewed specification and assessment of the equivalence of the batches tested in all the mammalian toxicity studies compared to the representative specification. This is particularly important because the concentration of the carcinogenic impurity PCA in the batch tested in the carcinogenicity studies is still unknown.

3. The presence of PCA and its structural precursor CPU in the metabolic pathway in plants and livestock has been demonstrated in the metabolism studies in apples and mushrooms, and in goat and hen, respectively. Potential exposure to PCA as a residue should be considered *a priori* as a concern since a threshold for a genotoxic carcinogen cannot be assumed.
   In case the margin of exposure (MoE) approach were to be applied for consumer dietary risk assessment of carcinogenic genotoxic metabolites, toxicological data and residue data in food of plant and animal origin are insufficient to perform the MoE assessment.

3. Overview of the concerns identified for each representative use considered

In addition to the concerns indicated in the table, all columns are grey as the technical material specification proposed was not comparable to the material used in the testing that was used to derive the toxicological reference values.

Representative use		Apples and pears	Mushrooms	Forestry
Operator risk	Risk identified			
	Assessment not finalised			
Worker risk	Risk identified			
	Assessment not finalised	X[1]	X[1]	X[1]
Bystander risk[(a)]	Risk identified			
	Assessment not finalised	X[1]	X[1]	X[1]
Consumer risk	Risk identified	X[3]	X[3]	X[3]
	Assessment not finalised			

The superscript numbers in this table relate to the numbered points indicated in sections 1 and 2.
[(a)] It was concluded that the potential risk is for residents that could be exposed to longer period of time compared to bystanders.

REFERENCES

EFSA (European Food Safety Authority), 2009. Conclusion regarding the peer review of the pesticide risk assessment of the active substance diflubenzuron. EFSA Scientific Report (2009) 332, issued on 16 July 2009.

EFSA (European Food Safety Authority), 2012a. Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578[5pp.].

EFSA (European Food Safety Authority), 2012b. Peer Review Report to the conclusion regarding the peer review of the pesticide risk assessment of confirmatory data submitted for the active substance diflubenzuron.

European Commission, 2009. Guidance document on the procedures for submission and assessment of confirmatory data following inclusion of an active substance in Annex I of Council Directive 91/414/EEC. SANCO 5634/2009 rev.3.

JMPR, 2002. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues Rome, Italy, 16-25 September 2002, Report 2002, 425 pp.

Sweden, 2011. Addendum to the Draft Assessment Report, confirmatory data, December 2011.

APPENDICES

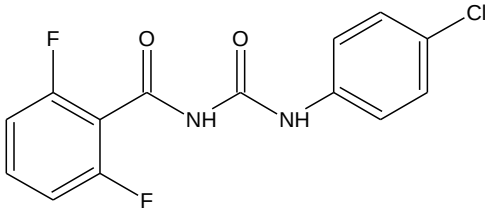
APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

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

Active substance (ISO Common Name) ‡	diflubenzuron
Function (e.g. fungicide)	insecticide

Rapporteur Member State	Sweden
Co-rapporteur Member State	Not relevant

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea
Chemical name (CA) ‡	N-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluorobenzamide
CIPAC No ‡	339
CAS No ‡	35367-38-5
EC No (EINECS or ELINCS) ‡	252-529-3
FAO Specification (including year of publication) ‡	None for TC
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	4-chloroaniline (PCA), CAS No.: 106-47-8, EEC No.: 203-401-0: maximum content can not be determined based on available data.
Molecular formula ‡	$C_{14}H_9ClF_2N_2O_2$
Molecular mass ‡	310.7
Structural formula ‡	

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	227.6 °C ± 0.3 °C, purity >99.5%
Boiling point (state purity) ‡	257 °C ± 0.5 °C at 40 kPa, purity 99.1%
Temperature of decomposition (state purity)	Not applicable, since no decomposition occurs at the melting point or the boiling point
Appearance (state purity) ‡	Physical state and colour: White (Munsell Notation N 9.5/) crystalline solid consisting of very fine needle-like crystals, purity 99.1% and 99.9% Odour: Faint, characteristic of aromatic compounds, at room temperature, purity 99.1%
Vapour pressure (state temperature, state purity) ‡	≤ 1.2 x 10^{-7} Pa at 25 °C, purity >99.5%
Henry's law constant ‡	≤ 4.7 x 10^{-4} Pa m^3 mol^{-1}
Solubility in water (state temperature, state purity and pH) ‡	purity >99.5% pH 4: 10 x 10 -5 g/L at 25 °C pH 7: 8 x 10 -5 g/L at 25 °C pH 10: 32 x 10-5 g/L at 25 °C
Solubility in organic solvents ‡ (state temperature, state purity)	purity 99.1->99.5% n-hexane: 0.063; toluene: 0.29; dichloromethane: 1.8; methanol: 1.1; acetone: 6.98; ethyl acetate: 0.48 (g/L at 20 ± 0.5 °C)
Surface tension ‡ (state concentration and temperature, state purity)	Not applicable, since the solubility in water is less than 1 mg/L
Partition co-efficient ‡ (state temperature, pH and purity)	At pH 3 and 22 °C ± 0.1°C Diflubenzuron: log P_{ow} = 3.89, purity 97.6% CPU: log P_{ow} =1.14 DFBA: log P_{ow} =-0.02
Dissociation constant (state purity) ‡	No data available-justification accepted
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	In acetonitrile, purity 99.9% λ_{max}: 257 nm; ε: 15148 l x mol^{-1} x cm^{-1} at 290 nm; ε: 10500 l x mol^{-1} x cm^{-1}
Flammability ‡ (state purity)	Not highly flammable and does not self-ignite, purity 99.1%
Explosive properties ‡ (state purity)	Not explosive, purity 99.1%
Oxidising properties ‡ (state purity)	Not oxidizing, purity 99.1%

Summary of representative uses evaluated (diflubenzuron)*

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		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)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Apples and pears	EU	Dimilin WG 80	F	Apple rust mite, Codling moth, Leafminers, Leafrollers, Pear suckers	WG	800 g/kg	Tractor-mounted and Hand-held sprayer*	Spring or autumn application depending on the pest to be controlled	max. 2	14-28 days	0.012	1500	0.18	14 days	Major crop The environmental risk assessment could not be concluded due to data gaps The consumer risk assessment could not be concluded due to data gaps.
Mushrooms	EU	Dimilin WG 80	I	Sciarid flies	WG	800 g/kg	Automatic and Hand-held sprayer	Course spray: Immediate after casing	1 per crop cycle	N.A.	0.1	1-1.5 L/m^2	1 g a.s./m^2	N.A.	Minor crop Environmental risk assessment not concluded due to data gaps The consumer risk assessment could not be concluded due to data gaps.
Forestry	EU	Dimilin WG 80	F	Various Lepidopterous and non-Lepidopterous forest pests	WG	800 g/kg	Aerial application, including ULV and LV	Dependent on pest to be controlled	max. 1	N.A.	1.6 0.16	3-5 30-50	0.048	N.A.	The environmental risk assessment could not be concluded due to data gaps. The consumer risk assessment could not be concluded due to data gaps. [2]
							Ground application with tractor mounted** or hand-held spray				0.008	600			

*Exposure assessment to surface water for the application with hand held sprayer is not finalized.
**Exposure assessment to surface water for the application with the tractor mounted sprayer is not finalized.
[1] A high risk and/or data gaps were identified in section 5 (ecotoxicology)
[2] The environmental risk assessment could not be finalised because no exposure assessment was available (data gap identified in section 4, fate and behaviour)..

Impact on Human and Animal Health

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

Rate and extent of oral absorption ‡	Oral absorption approx. 33%, based on urinary excretion
Distribution ‡	Uniformly distributed
Potential for accumulation ‡	No evidence of accumulation
Rate and extent of excretion ‡	Excretion almost complete in 24 hours
Metabolism in animals ‡	Extensively metabolised (approx.40% by dechlorination, glucuronidation, sulphation and hydrolysis).
Toxicologically relevant compounds ‡ (animals and plants)	Parent compound, PCA and metabolites
Toxicologically relevant compounds ‡ (environment)	Parent compound

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	> 4640 mg/kg bw	
Rat LD_{50} dermal ‡	> 2000 mg/kg bw	
Rat LC_{50} inhalation ‡	> 2.5 mg/L, 4h (nose-only, dust)	
Skin irritation ‡	Non-irritant	
Eye irritation ‡	Non-irritant	
Skin sensitisation ‡	Non-sensitizer (Magnusson &Kligman)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Haemolytic anaemia	
Relevant oral NOAEL ‡	Rat (90-day): 11 mg/kg bw per day Mouse (90-day): 9.7 mg/kg bw per day Dog (1-year): 10 mg/kg bw per day	
Relevant dermal NOAEL ‡	Rat (21-day): 1000 mg/kg bw per day (highest dose level tested). Rabbit (3-weeks): 322 mg/kg bw per day (highest dose level tested).	
Relevant inhalation NOAEL ‡	Rat (4-weeks): 0.1 mg/L (highest dose level tested). Rabbit (3-weeks): 1.9 mg/L (highest dose level tested).	

Genotoxicity ‡ (Annex IIA, point 5.4)

No genotoxic potential	

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

Target/critical effect ‡	Haemolytic anaemia	
Relevant NOAEL ‡	Rat (2-years): 31 mg/kg bw/d Mouse (91-weeks): 6.4 mg/kg bw/d	
Carcinogenicity ‡	No carcinogenic potential	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	No effect on reproduction Parental: Haemolytic anaemia No effects on the offspring	
Relevant parental NOAEL ‡	LOAEL: 30 mg/kg bw per day (lowest dose level tested)	
Relevant reproductive NOAEL ‡	3200 mg/kg bw per day (highest dose level tested)	
Relevant offspring NOAEL ‡	3200 mg/kg bw per day (highest dose level tested)	

Developmental toxicity

Developmental target / critical effect ‡	No developmental, no maternal effects	
Relevant maternal NOAEL ‡	Rat & rabbit NOAEL: 1000 mg/kg bw per day (highest dose level tested)	
Relevant developmental NOAEL ‡	Rat & rabbit NOAEL: 1000 mg/kg bw per day (highest dose level tested)	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data, no study required	
Repeated neurotoxicity ‡	No data, no study required	
Delayed neurotoxicity ‡	No data, no study required	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	No data, no study required
Studies performed on metabolites or impurities	CPU and DFBAM: Limited information available, further information / evaluation required.
	PCA: *In vivo* genotoxic agent. Carcinogenic (Carc. Cat.2).

Medical data ‡ (Annex IIA, point 5.9)

No evidence of adverse effects to workers of manufacturing plants, agricultural worker and consumers

Summary (Annex IIA, point 5.10) **Diflubenzuron**	Value	Study	Safety factor
ADI ‡	0.1 mg/kg bw per day	1 year dog	100
AOEL ‡	0.033 mg/kg bw per day	1 year dog	100 (33 % oral abs)
ARfD ‡	Not allocated- not necessary		

Summary (Annex IIA, point 5.10) **PCA**	Value	Study	Safety factor
ADI, AOEL, ARfD ‡	Cannot be set because a threshold for a genotoxic carcinogen cannot be assumed.		
Reference point as basis for margin of exposure	Toxicological data available not sufficient.		

Dermal absorption ‡ (Annex IIIA, point 7.3)	
Formulation (Dimilin WG-80)	Active substance tested considered to be representative for the formulation. Concentrate and spray dilution: 6% Rat *in vivo* study

Exposure scenarios (Annex IIIA, point 7.2)	
Operator	Pome fruit: Tractor-mounted sprayer UK POEM: 66% of AOEL with gloves during mixing and loading and during application. German model: 52% of AOEL without PPE. Hand-held sprayer UK POEM: 19% of AOEL with gloves during mixing and loading and during application. German model: 31% of AOEL without PPE Forestry: German model Ground application - tractor mounted sprayer 14 % of AOEL without PPE Ground application – hand held sprayer 8 % of AOEL without PPE Aircraft Application: inconclusive. Mushrooms: German model Automatic sprayer 83 % of AOEL without PPE Hand-held sprayer 46 % of AOEL with gloves during mixing and loading and gloves, coverall and sturdy footwear during spraying
Workers	Pome fruit: 59% of AOEL Forestry: 4% of AOEL Mushrooms: 10 % of AOEL Worker risk assessment to PCA as residue inconclusive in all scenarios as exposure data are missing.

Bystanders	Pome fruit: 3.5 % of AOEL Forestry: ≤3.5 % of AOEL Mushrooms: Not relevant Bystander/resident risk assessment to PCA as residue inconclusive in all scenarios as exposure data are missing.

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

	RMS/peer review proposal
Substance (name)	RMS: No classification

Residues

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

Plant groups covered	Fruit group (apples and oranges) after foliar treatment, and fruit group (mushrooms) after soil treatment (growth medium/casing).
Rotational crops	Not applicable (a)
Metabolism in rotational crops similar to metabolism in primary crops?	Not applicable (a)
Processed commodities	A data gap concerning a hydrolysis study has been formulated. Concerning mushrooms it was decided that the main component in mushrooms DFBA is not expected to metabolize further during processing. Therefore, it was decided that no study on the effect of processing on the nature of residues is necessary.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	No information on the effect of processing on the nature of residues for apples is available (data gap). The main component in mushrooms DFBA is not expected to metabolize further during processing.
Plant residue definition for monitoring	For fruit crops after foliar application: Diflubenzuron For mushrooms after soil application: 2,6-difluorobenzoic acid (DFBA)
Plant residue definition for risk assessment	For fruit crops after foliar application (provisional): (1) Diflubenzuron (2) Sum of 4-chlorophenylurea (CPU) + 4-chloroaniline (PCA) expressed as 4-chloroaniline; pending the finalisation of the toxicological evaluation of the metabolite CPU. For mushrooms after soil application (provisional): (1) Sum of diflubenzuron and 2,6-difluorobenzoic acid (DFBA) expressed as diflubenzuron (2) Sum of 4-chlorophenylurea (CPU) + 4-chloroaniline (PCA) expressed as 4-chloroaniline; pending the finalisation of the toxicological evaluation of the metabolite CPU. Note: CPU is a structural precursor to PCA; data and information is currently insufficient to have a firm view on the toxicity of CPU in humans and on its behaviour and magnitude in raw and processed food commodities
Conversion factor (monitoring to risk assessment)	None

(a) EFSA notes that if the further evaluation in the fate section shows that significant residues of diflubenzuron or its metabolites are expected on agricultural land where mushroom compost has been used, the possible occurrence of residues in crops grown on such agricultural land has to be addressed also.

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

Animals covered	Poultry (laying hen) and ruminants (lactating goat)

Time needed to reach a plateau concentration in milk and eggs	Milk: The metabolism study was carried out for 3 days only. It is not possible to conclude if a plateau was reached during this time. Egg white: 2.5 days Egg yolk: 7.5 days
Animal residue definition for monitoring	Diflubenzuron and 4-chlorophenylurea (CPU) expressed as diflubenzuron
Animal residue definition for risk assessment	Provisional**:** 1) Diflubenzuron 2) Sum of 4-chlorophenylurea (CPU) + 4-chloroaniline (PCA) + 4-chloroacetanilide (PCAA) expressed as 4-chloroaniline pending the finalisation of the toxicological evaluation of the metabolites CPU and PCAA
Conversion factor (monitoring to risk assessment)	None
Metabolism in rat and ruminant similar (yes/no)	Yes.
Fat soluble residue: (yes/no)	Yes.

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

Not applicable (a)

(a) EFSA notes that if the further evaluation in the fate section shows that significant residues of diflubenzuron or its metabolites are expected on agricultural land where mushroom compost has been used, the possible occurrence of residues in crops grown on such agricultural land has to be addressed also.

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

Apples: Diflubenzuron was stable for 12 months at –18 °C. Mushrooms: Diflubenzuron was stable for 18 months at – 18 °C 4-chlorophenylurea was stable for 19 months at –18 °C, 4-chloroaniline was not stable under theses conditions: Notifier to investigate the stability of 4-chloroaniline during frozen storage (data gap). Studies on the storage stability of diflubenzuron, 4-chlorophenylurea and 4-chloroaniline are available in the DAR as part of the metabolism study on livestock. EFSA notes that the presentation of the results in the DAR does not allow full evaluation of the validity of these studies and their results. If they are needed to support feeding studies in livestock, full evaluation will be necessary.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)
The dietary burden calculation could not be finalised, as the study on the effect of processing on the nature of residues was outstanding and the residue definition for risk assessment for animal matrices was not finalised. The meeting carried out a provisional dietary burden calculation considering the intake of diflubenzuron only. For a STMR for apples of 0.41 mg/kg and a mean processing factor for apples to pomace of 3.2 the following intake was calculated: 0.6 mg/kg feed (DM) for diary cattle and 1.7 mg/kg feed (DM) for beef cattle.

Data gap: Notifier to provide either a feeding study in ruminants or a justification on the basis of the metabolism study showing that a feeding study is not required.

	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)			
Potential for accumulation (yes/no):			
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)			
	Feeding studies Residue levels in matrices : Mean (max) mg/kg		
Muscle			
Liver			
Kidney			
Fat			
Milk			
Eggs			

Summary of residues data according to the representative uses on raw agricultural commodities and feeding stuffs (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	Northern	0.10, 2 x 0.16, 0.20, 0.32, 0.39, 0.43, 0.44, 0.45, 0.50, 2 x 0.52	Only four of the trials were performed with Dimilin WG 80, the other was performed with Dimilin 25 WP. However bridging studies in whole fruit and processed fruit did not show any significant difference in residues between the 2 formulations. EFSA notes that four of the trials were carried out as parallel trials comparing two different formulations of diflubenzuron. However, deletion of the lower results of each of the parallel trials would not significantly change the overall results.	1.0	0.52	0.41
	Southern	0.24, 0.35, 0.35, 0,35, 0.37, 0.41, 0.46, 0.55	All trials were performed with Dimilin 25 WP Note: To comply with the residue definition for risk assessment, residue trials in apples/pears analysing for CPU and PCA with a sufficiently low LOQ would be necessary, if the MOE approach was to be applied for consumer risk assessment.	1.0	0.55	0.36
Mushrooms	Green houses indoor		The submitted trials were not carried out in accordance with the proposed			

			residue definition. Data gap: A complete data base of residue trials on mushrooms in compliance with the residue definition for risk assessment is necessary.			

(a) Numbers of trials in which particular residue levels were reported e.g. 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(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

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

Part 1) Diflubenzuron[9]

ADI	0.1 mg/kg bw per day
TMDI (% ADI) according to WHO European diet	-
TMDI (% ADI) according to EFSA PRIMO rev.2 model diets	Maximum TMDI[10] DE Child: **13,7%** NL Child: **7,4%**
IEDI (WHO European Diet) (% ADI) NEDI (specify diet) (% ADI)	Not applicable since TMDI calculations demonstrate that the ADI will no be exceeded
Factors included in IEDI and NEDI	Not applicable
ARfD	No ARfD is established
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

Part 2) Sum of CPU and PCA expressed as PCA for food of plant origin/ Sum of CPU, PCAA and PCA expressed as PCA for food of animal origin

In the absence of toxicological data, as a precautionary approach, CPU and PCAA were provisionally included in this part of the residue definition based on their structural similarity and, for CPU, the potential to be further degraded or metabolised to PCA.
Exposure to PCA should be considered *a priori* as a concern since a threshold for a genotoxic carcinogen cannot be assumed. The available toxicological database for PCA and the available residue data do not permit conducting a MoE assessment.

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	Yield factor	
Apple wet pomace	3	3.2 (a)		
Apple juice	3	<0.2 (a)		
Apple raw Juice	3	<0.2 (a)		
Apples puree	3	<0.2 (a)		
Mushrooms	(b)			

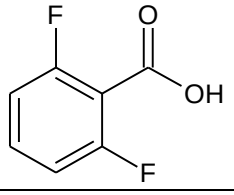
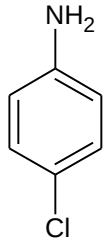
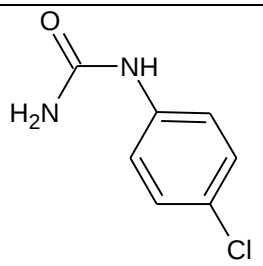
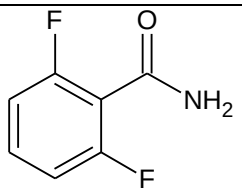
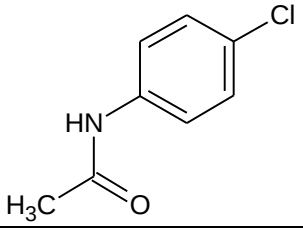
(a) Provisional: depending on the results of the hydrolysis study (data gap) new processing studies may be necessary.
(b) The submitted studies have not been carried out in accordance with the proposed residue definition in mushrooms. EFSA notes that the necessity of processing studies on mushrooms in accordance with the residue definition should be decided when new residue data on mushrooms and the consumer risk assessment for the consumption of mushroom are available.

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

Apple, Pear	1.0 mg/kg
Mushrooms	Unable to propose - Data insufficient
Food of animal origin	Unable to propose - Data insufficient

[9] Mushrooms (Sum of diflubenzuron and DFBA expressed as diflubenzuron) not included in RA due to insufficient data
[10] Based on MRL for apple/ pear and a value of 0.5 mg/kg for berries/small fruits to cover wild berries (Forestry use)

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name*	Chemical name	Structural formula
DFBA	2,6-difluorobenzoic acid	
PCA	4-chloroaniline	
CPU	4-chlorophenylurea	
DFBAM	2,6-difluorobenzamide	
PCAA	4-chloroacetanilide	

ABBREVIATIONS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
AVD	avoidance delay time
AVT	avoidance threshold dose
bw	body weight
CA	Chemical Abstracts
CAS	Chemical Abstracts Service
CIPAC	Collaborative International Pesticides Analytical Council Limited
d	day
DAR	draft assessment report
DNA	deoxyribonucleic acid
DM	dry matter
DT_{50}	period required for 50 percent degradation / dissipation
DT_{90}	period required for 90 percent degradation / dissipation
ε	decadic molar extinction coefficient
EC_{50}	effective concentration, median
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FPM	feeding rate per minute
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
g	gram
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
HD_5	fifth percentile of the distribution of LD_{50}s between species
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high performance liquid chromatography or high pressure liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
k	metabolic rate
kg	kilogram
K_{oc}	organic carbon adsorption coefficient
L	litre
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
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEL	lowest observed effect level
LOQ	limit of quantification (determination)
µg	microgram

mN	milli-Newton
MAF	multiple application factor
Min	minute
MoE	margin of exposure approach
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated Short Term Intake
NIR	Near-Infrared-(Spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PD	proportion of food type in diet
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
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
PT	proportion of diet obtained in the treated area
r^2	coefficient of determination
RA	Risk assessment
RMS	rapporteur Member State
RUD	residue per unit dose
SCFCAH	Standing Committee on the Food Chain and Animal Health
SL	Soluble concentrate
SSD	species sensitivity distribution
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
TWA	time weighted average
UDS	unscheduled DNA synthesis
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year