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

carbosulfan

finalised: 28 July 2006

SUMMARY

Carbosulfan is one of the 52 substances of the second stage of the review programme covered by Commission Regulation (EC) No 451/2000[1], as amended by Commission Regulation (EC) No 1490/2002[2]. This Regulation requires the European Food Safety Authority (EFSA) 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 one year a conclusion on the risk assessment to the EU-Commission.

Belgium being the designated rapporteur Member State submitted the DAR on carbosulfan in accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, which was received by the EFSA on 11 August 2004. Following a quality check on the DAR, the peer review was initiated on 17 August 2004 by dispatching the DAR for consultation of the Member States and the sole applicant FMC Chemical sprl. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed in an evaluation meeting on 18 May 2005. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in September 2005.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 8 June 2006 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as insecticide as proposed by the applicant which comprises incorporation into soil (at drilling) to control soil insects, where maize and sugar beet will be grew. The application rate is 0.75 kg carbosulfan per hectare. Carbosulfan can be used as insecticide and nematicide. It should be noted that during the peer review process only the use as insecticide was evaluated.
The representative formulated product for the evaluation was "Marshal 10G", a granule (GR), registered in some Member States of the EU.

[1] OJ No L 53, 29.02.2000, p. 25
[2] OJ No L 224, 21.08.2002, p. 25

It should be noted that the applicant no longer supports the second formulation, presented in the dossier and DAR ("Marshal 25CS"). Consequently the uses on citrus and cotton are no longer supported.

Adequate methods are available to monitor all compounds given in the respective residue definition for food of plant origin, soil and water.
Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that at least limited quality control measurements of the plant protection product are possible.

Carbosulfan is toxic if swallowed and should be classified as T, R25 “Toxic if swallowed”. It is of low toxicity via dermal route and toxic via inhalation (classification as T, R23 is proposed).
Carbosulfan is not a skin or eye irritant but is a skin sensitiser and should be classified R43 “May cause sensitisation by skin contact”. Carbosulfan gave negative results in in vitro and in vivo genotoxicity tests and did not show any carcinogenic potential. Nevertheless, the level of impurities in batches used for toxicological studies remains a concern. In the three-generation rat study, the relevant maternal and reproductive NOAEL was 1.2 mg/kg bw/day. In developmental toxicity studies in rats and rabbits, the relevant maternal and developmental NOAEL was 2 mg/kg bw/d. Carbosulfan displayed no potential for induced delayed neurotoxicity. The provisional reference values are as follows: ADI and ARfD are 0.01 mg/kg bw/day; AOEL is 0.02 mg/kg bw/day. The risk assessment for operators has to be considered as inconclusive until the AOEL is confirmed. However, it can be assumed that bystander and worker exposure is likely to be negligible under the supported conditions of use.

The metabolism, distribution and residue behaviour of carbosulfan was investigated in various crops with different methods of application. Based on these studies the metabolic pathway of carbosulfan in plants can be considered as sufficiently investigated. At the time being, carbosulfan, carbofuran and 3-OH-carbofuran were considered the relevant residues to assess consumer exposure and consumer risk. However, the metabolite dibutylamine is still under discussion concerning its possible genotoxicity and ought to be therefore considered a potential candidate to include in the residue definition, too. Moreover a need to address residues of dibutylamine but also carbofuran and its metabolites in succeeding crops following application of carbosulfan was identified.

Based on the currently proposed residue definition, supervised residue trials in sugar beet and maize indicated that residues were low and mostly below the respective LOQ. However, the available residue trials have to be reconsidered for their validity and sufficiency. With regard to the metabolite dibuytlamine no residue data have been reported. Further residue data in cotton seed and citrus will be needed if foliar uses are reinstated in the future.

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Since the assessment of plant residues still needs to be finalized and due to the lack of peer reviewed evaluation of relevant data and information it is not possible to conclude on whether or not significant residues may occur in edible animal matrices.
The consumer risk assessment should be considered as inconclusive due to the uncertainties caused by lacking data identified during the evaluation.

In soil under laboratory aerobic conditions, carbosulfan yields carbofuran (max. 48.7 % - 69.3 % AR after 7 d). Also 3-keto-carbofuran is produced in significant amounts (max. 5.3 % - 6.6 %) and needs to be further assessed as it contains the active carbamate moiety. The mineralization was very limited and bounded residues increased up to maximum of 90 % AR after 100 d. In a study performed with 14C-dibutylamine labelled carbosulfan, dibutylamine was found as a major aerobic soil metabolite.
No valid degradation study of carbosulfan in soil under anaerobic conditions is available. Also photolysis in soil was not investigated. Metabolite carbofuran was considered stable to photolysis in soil in its DAR.
Evaluation meeting agreed that a re-evaluation of the degradation kinetic in degradation studies had to be performed. Reassessment is available but has not been evaluated and peer reviewed. Therefore, end points for laboratory soil degradation of carbosulfan have not been established.
Summaries of some field dissipation studies in EU are available. Half life of carbosulfan in these trials ranges between 0.35 to 31.3 d and half life of carbofuran is between 1.3 to 71.9 d. EFSA notes that, in the context of the carbofuran discussion, the meeting of MS experts was not able to determine the reliability of these studies. A position paper is available (June 2005) but has still not been assessed and peer reviewed. PEC in soil were calculated in the DAR for carbosulfan and carbofuran based on the field worst case half lives and the representative uses in maize, sugar beet, citrus and cotton. Evaluation meeting agreed that half life and PEC soil of dibutylamine need to be determined. A position paper is already available but has not been evaluated and peer reviewed.
The rapporteur Member State concluded that the soil adsorption / desorption study is of limited quality. The meeting of MS experts agreed that the study was not valid and identified a data gap for a valid study for carbosulfan and dibutylamine. For the metabolite carbofuran an additional study (from a different notifier Dianica) is available in its dossier as active substance.
A lysimeter study is available. However, annual average concentrations and detailed characterization of the residue are missing. Evaluation meeting agreed that levels of dibutylamine need to be determined in the leachate samples and that the two new lysimeters performed with carbofuran should be submitted and assessed. These studies and a position paper are already available but have not been evaluated and peer reviewed.
Carbosulfan hydrolyses with half lives lower than 1 d at pH 5 and 7 and of 7 d at pH 9. Main products are carbofuran and dibutylamine. Carbofuran degrades to carbofuran-7-phenol.
Photolysis may contribute to the environmental degradation of carbosulfan in water. Two regions of polar degradation products (66.7 % AR) were found but not characterized. Their environmental relevance is uncertain and was not examined by the meeting of MS experts since the study was still not evaluated. Carbosulfan is not readily biodegradable.

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Carbosulfan was low persistent in aerobic water / sediment systems. Main metabolites formed were carbofuran (max. 34.7 % AR in water; max. 20.1 % AR in sediment) and carbofuran-7-phenol (max. 11.6 % AR in water; max. 3.21 % AR in sediment). A non characterized metabolite (Unknown 3) appears at levels above 10 % AR in the sediment of some systems (max. 20.11 % AR after 7 d). This compound has been tentatively identified as a structure that contains the carbamate moiety and may be expected to produce carbofuran when degraded. The amount of bound residues increased steadily up to 30.5 – 43.0 % AR at the end of the experiments (102 d).

No half lives are reported in carbosulfan DAR for metabolites carbofuran and carbofuran-7-phenol in the water / sediment systems. From water / sediment studies summarized in the carbofuran DAR, carbofuran degraded in the whole system with a first order half life of approximately 41 d. Available water sediment studies under alkaline conditions (from carbofuran applicant Dianica) show a faster degradation of carbofuran and the formation of carbofuran-7-phenol at high levels.

PECSW/SED were calculated by the applicant based on an ad hoc modelling exercise. Evaluation Meeting confirmed the rapporteur Member State data requirement for FOCUS SW PECSW/SED and agreed that PECSW for dibutylamine need to be calculated. FOCUS SW calculations and a position paper for dibutylamine are available but have not been evaluated and peer reviewed.

The applicant presented an estimation of the potential for ground water contamination based on the FOCUS GW scheme (PRZM). The rapporteur Member State considered that half life and Koc employed for carbofuran in the calculation were not justified and proposed a data requirement for new PECGW. This data requirement was confirmed by the Evaluation Meeting that additionally required calculation of PECGW for metabolite dibutylamine. New FOCUS GW calculations for carbofuran and a position paper for dibutylamine are available but have not been evaluated and peer reviewed. Additionally, experts meeting indicated that potential ground water contamination by soil metabolite 3-keto-carbofuran should be addressed.

It is not expected that neither carbosulfan nor its transformation product carbofuran (from data in carbofuran dossier) may contaminate the air compartment or be prone to long range transport through air.

An addendum to the fate and behaviour chapter has been provided on 18 May 2006. When reported, the information in the addendum has been summarized too briefly to draw any conclusion on its reliability. Studies or reports presumably submitted by the applicant are not adequately referenced. Therefore studies submitted by the applicant after the DAR was submitted are considered neither evaluated nor peer-reviewed in this conclusion.

The first tier risk assessment based on generic species identified a potential risk to insectivorous birds in citrus and cotton, to medium herbivorous birds in cotton and to small herbivorous mammals in citrus from foliar application of carbosulfan. Only a small number of granules have to be ingested by a small bird to reach the acute LD50 or the LC50, hence the risk of ingestion of granules should be further addressed. The number of granules that have to be ingested by a small mammal to reach the LD50 is relatively high and since granules are not attractive to mammals the acute risk is considered to be low. Few granules are however needed to reach the NOAEL for mammals and the long-term

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risk needs to be further addressed. Also the risk from ingestion of treated seedlings, contaminated earthworms, fish and drinking water needs to be evaluated.

Carbosulfan and the metabolite carbofuran are classified as very toxic to aquatic organisms. For citrus and cotton the risk assessment indicates acute and long-term risk to aquatic organisms even with 50 m buffer zones based on contamination by spray drift only. Based on available data for PECsw, a long-term risk is indicated for all representative uses evaluated from exposure to the metabolite carbofuran via drainage to surface water. The assessment needs to be refined based on FOCUS modelling of PECsw.

Carbosulfan is toxic to bees. For the representative uses in citrus and cotton the risk needs to be further addressed by semi-field or field tests. Since sugar beet crop is not flowering the risk from the use in sugar beet is considered low. The risk to bees from exposure to carbosulfan/carbofuran in nectar and pollen following granular application was not assessed due to non evaluated data on oral toxicity for carbofuran. Laboratory studies confirm that carbosulfan is toxic to arthropods. Further semi-field or field studies are required to evaluate the risk. The risk to earthworms from the use of MARCHAL 25 CS is considered as low. For the granular formulation further clarification is needed on whether the field study with MARCHAL 25 CS can be used for the assessment. No evaluation of the risk to soil micro-organisms and non-target plants is available. For biological methods of sewage treatment the risk is considered to be low.

Key words: carbosulfan, peer review, risk assessment, pesticide, insecticide, nematicide

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BACKGROUND

Commission Regulation (EC) No 451/2000 laying down the detailed rules for the implementation of the second and third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC, as amended by Commission Regulation (EC) No 1490/2002, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Carbosulfan is one of the 52 substances of the second stage covered by the amended Regulation (EC) No 451/2000 designating Belgium as rapporteur Member State.

In accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, Belgium submitted the report of its initial evaluation of the dossier on carbosulfan, hereafter referred to as the draft assessment report, to the EFSA on 11 August 2004. In accordance with Article 8(5) of the amended Regulation (EC) No 451/2000 the draft assessment report was distributed for consultation on 17 August 2004 to the Member States and the main applicant FMC Chemical sprl 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, representatives from Member States identified and agreed in an evaluation meeting on 18 May 2005 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level. A representative of the notifier attended this meeting.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings organised on behalf of the EFSA by the EPCO-Team of the Pesticide Safety Directorate (PSD) in York, United Kingdom in September 2005. 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 with representatives from Member States on 8 June 2006 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 Health, Plant Protection Products and their Residues (PPR).

In accordance with Article 8(7) of the amended Regulation (EC) No 451/2000, 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 08 June 2005)
- the consultation report

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 19 June 2006)

Given the importance of the draft assessment report including its addendum (compiled version of May 2006 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

Carbosulfan is the ISO common name for 2,3-dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio)methylcarbamate (IUPAC).

Carbosulfan belongs to the class of benzofuranyl methylcarbamate insecticides such as benfuracarb and carbofuran. It belongs also to the class of carbamate nematicides. Carbosulfan is a systemic insecticide with contact and stomach action. The biological activity is based on a cleavage of the S-N-carbamate bond, which leads to the formation of carbofuran. Carbofuran inhibits the cholinesterase in the nervous system.

The representative formulated product for the evaluation was "Marshal 10G", a granule (GR), registered in some Member States of the EU.
It should be noted that the applicant no longer supports the second formulation, presented in the dossier and DAR ("Marshal 25CS"). Consequently the uses on citrus and cotton are no longer supported.

The evaluated representative uses as insecticide comprise incorporation into soil (at drilling) to control soil insects, where maize and sugar beet will be grew. The application rate is 0.75 kg carbosulfan per hectare. Carbosulfan can be used as insecticide and nematicide. It should be noted that during the peer review process only the use as insecticide was evaluated.

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SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of carbosulfan as manufactured should not be less than 890 g/kg (before adding the stabilizer), which is higher than the minimum purity given in the FAO specification 417/TC/S/F (1991) of 865 g/kg. The higher value relates to the submitted results of current batch analysis and not to any toxicological concern to increase the minimum purity.
The minimum purity of the technical material containing the stabilizer should not be less than 865 g/kg. No explicit FAO specification exists for technical material containing a stabilizer.

The technical material contains three impurities which have to be regarded as relevant: carbofuran, 5-chlorocarbofuran and *N*-nitrosodibutylamine. The maximum content in the technical material should not be higher than 20 g/kg for carbofuran and 2 g/kg for 5-chlorocarbofuran, respectively. For the moment it is not possible to set a maximum level for *N*-nitrosodibutylamine. Only carbofuran is mentioned in the FAO specification. The relevance of a fourth impurity is still under discussion (refer to 2.4 and 2.8).

However, since clarification is required with respect to the analytical methods for the determination of the impurities (relevant as well as significant) in the technical material, the specification for the technical material as a whole should be regarded as provisional for the moment.

Beside this, 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 carbosulfan or the respective formulation. However, the following data gap was identified:
- Spectra for the relevant impurity 5-chlorocarbofuran and *N*-nitrosodibutylamine.

Furthermore, it should be noted that the data on the tap density and the accelerated storage (content of carbosulfan) are not in line with the FAO specification 417/GR/S/F (1991)[3].
In addition to this, no information is available that demonstrate that the content of the relevant impurity 5-chlorocarbofuran and *N*-nitrosodibutylamine in the technical material are not increasing in the formulation upon storage. Data for carbofuran are available and demonstrate that the content of carbofuran is within the limits of the FAO specification (417/GR/S/F; 1991).

The content of carbosulfan in the representative formulation is 100 g/kg (pure).

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

[3] The applicant indicated that activities have been initiated to adapt the FAO specification.

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Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of carbosulfan in the technical material and in the representative formulation. Addition validation data for the method used for the determination of the impurities in the technical material are required (full validation for impurities 6 and 5-chlorocarbofuran; accuracy for the other impurities). Therefore, no validated analytical method is available for the determination of the relevant impurity 5-chlorocarbofuran.
Beside this, the assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the analytical methods.

However, sufficient test methods and data relating to physical, chemical and technical properties and analytical methods are available to ensure that at least limited quality control measurements of the plant protection product are possible.

With respect to the residue analytical methods for enforcement purposes, adequate methods are available to monitor all compounds given in the respective residue definition, i.e. carbosulfan in food of plant origin; carbofuran (sum of carbofuran and 3-OH-carbofuran[4]) in food of plant origin; carbosulfan and carbofuran in surface water.
Also validated methods for the determination of carbofuran, carbosulfan and 3-OH-carbofuran in blood are available.
However, the applicability of the method for the determination of 3-OH-carbofuran in food must be confirmed by additional ILV data.
The residue definitions for soil and ground water are still under discussion. Depending on further assessment, 3-keto-carbufuran[5] and dibutylamine could be included in the residue definition for ground water and 3-keto-carbufuran in the definition for soil.
An analytical method for the determination of residues in air is not required according to SANCO/825/00, due to the application technique (i.e. granular formulation to be incorporated in soil) is such that no relevant exposure is likely to occur). However, a method for the determination of carbosulfan is available.

The methodology used is GC with PN- or MS detection and HPLC with post column derivatisation and fluorescence detection. A multi-residue method like the Dutch MM1 or the German S19 is not applicable to due the nature of the residues.

An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed (see 3.2).

The discussion in the meeting of experts (EPCO 35, September 2005) on identity, physical and chemical properties and analytical methods was limited to the physical and chemical properties of

[4] 3-OH-carbofuran: 3-hydroxy-carbofuran; 3-hydroxy-2,3-dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio)methylcarbamate
[5] 3-keto-carbofuran: methyl carbamic acid 2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-7-yl ester

carbosulfan, certain properties of the representative formulation, the analytical methods and the relevance of two impurities.

Recently submitted studies, regarding additional validation data of impurity methods (full validation for impurities 6 and 5-chlorocarbofuran; accuracy for the other impurities) were not evaluated by the RSM yet.

2. Mammalian toxicology

Carbosulfan was discussed at EPCO experts' meeting for mammalian toxicology (EPCO 33) in September 2005.

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

Oral absorption after single low dose exposure is >70 % of the dose based on urinary excretion, exhaled air, tissues, and carcass. Carbosulfan is widely distributed, mainly in excretory organs and carcass. Excretion is rapid and extensive within 24 hours, mainly via urine (63-78%); no accumulation was evident. Metabolism is extensive (>80%): carbosulfan mainly undergoes hydrolysis to form 7-phenol and to form carbofuran products, which can be further metabolised.

2.2. Acute toxicity

The acute oral toxicity of carbosulfan has been evaluated in rats, rabbits and mice. Carbosulfan LD_{50} is 42.7 mg/kg bw, (rabbit), therefore classification as **T, R25 "Toxic if swallowed"** is proposed**.** Carbosulfan is of low toxicity via dermal route (dermal LD_{50} 3700 mg/kg bw in rats) and **"Toxic via inhalation"** (LC_{50} 0.61 mg/L): classification as **T, R23** is proposed.
Carbosulfan is not a skin or eye irritant but is a skin sensitiser and classification as **R43 "May cause sensitisation by skin contact"** is proposed.

2.3. Short term toxicity

Brain AChE is the most sensitive parameter following carbosulfan exposure, not always accompanied by overt clinical signs of toxicity.

In dogs, after a six-month exposure in diet, haematological parameters were altered and spleen relative weight decreased at doses lower than the ones inducing brain and plasma cholinesterase inhibition.
The relevant oral NOAEL is 20 ppm, equivalent 2 mg/kg bw/day, as agreed during the meeting.

The inhalation study showed a NOAEL of 0.00015 mg/L; the NOAEL for systemic toxicity in rabbits after 21 day dermal exposure is 5 mg/kg bw/day.
The experts' meeting concluded that no classification was required resulting from the repeated inhalation study, and was noted that carbosulfan was classified as toxic by inhalation already.

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EFSA notes: Recently, the rapporteur Member State confirmed the oral NOAEL of 20 ppm, but taking into account the measured food intake, the conversion lead to the new value of 1.2 mg/kg bw/day. This approach has not been discussed nor peer reviewed by MSs.

2.4. Genotoxicity

Carbosulfan gave negative results in *in vitro* tests. *In vivo*, carbosulfan was tested in a number of studies; however, the shortcomings of many of these studies make a scientific evaluation of the results difficult. In addition, results from the open literature did not add further information. A new *in vivo* chromosomal aberration test in mice giving clearly negative results was submitted and discussed during the meetings.
The meeting noted that carbosulfan technical has a proposed minimum purity of 89%. A stabiliser was added to the material used in toxicity studies, and as a result contained less impurities. The batches used in toxicity studies had reported purities of 90.8-94.7%. The rapporteur Member State indicated that the toxicological properties of the impurities carbofuran and dibutylamine were known. It was noted that the test material used in the *in vivo* chromosomal aberration study was 84%, and was assumed to be technical material (non stabilised). The issue was referred to the physical-chemical properties meeting in order to determine major differences in manufacturing process; and whether the impurity profile and five batch analysis justifies low purity.

Notifier was required to submit data on the presence of nitrosamine at concentration of 10-26 mg/kg in the technical active substance in the batches of carbosulfan used in genotoxicity studies.
EFSA note: the identified data gap might have a great impact on the risk assessment due the known toxicological properties of nitrosamines (see also 2.10 and 2.12).

2.5. Long term toxicity

One long-term study in rats and one in mice were provided. Target effect was the inhibition of brain and red blood cell acetyl cholinesterase.
In the rat study, focal iris atrophy and degenerative retinopathy observed were ascribed to exposure to carbosulfan. This effect was not observed in mice. The lowest relevant NOAEL is 1 mg/kg bw/day from the 2 year study in rats. Carbosulfan did not show carcinogenic potential.

Notifier was required to submit data on the presence of nitrosamine at concentration of 10-26 mg/kg in the technical active substance in the batches of carbosulfan used in carcinogenicity studies.
EFSA notes that the identified data gap might have a great impact on the risk assessment due the known toxicological properties of nitrosamines (see above).

2.6. Reproductive toxicity

In the three-generation rat study, parental toxicity consisted of decreased body weight and food consumption. Body weight of females was altered during gestation and lactation but not during the

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growing phase at high doses. At the highest dose, clear signs of foetotoxicity were seen in different litters (decreased body weight, body weight gain, and in some litters, number pups born alive and survival were significantly decreased). The relevant maternal and reproductive NOAEL was 1.2 mg/kg bw/day.

Carbosulfan administered to rats by gavage produced an incomplete ossification at maternally toxic doses (≥10 mg/kg bw/day); the relevant maternal and developmental NOAEL was 2 mg/kg bw/day. (The meeting confirmed the proposal of the rapporteur Member State to decrease the maternal NOAEL from 10 mg/kg bw to 2 mg/kg bw due to the consistent reduction in the number of pups born alive, pup weight and pup survival in the presence of maternal toxicity).
In relation to the incidence of major vessel variations in the rabbit developmental study, it was noted that the left carotid arises from the innominate, and that effects were sporadic and showed no dose response. This effect was therefore not considered treatment-related, and the developmental NOAEL in the rabbit study was increased from <2 mg/kg bw/day to 10 mg/kg bw/day.

A proposal for a classification was discussed since effects were noted, but not considered sufficient to warrant classification.

2.7. Neurotoxicity

Carbosulfan displayed no potential for development of clinical signs or morphologic changes associated with organophosphorus induced delayed neurotoxicity.
The experts set a new data requirement for the Notifier to submit acute and subchronic neurotoxicity studies that were submitted to FAO.
EFSA notes that the identified data gap might have an impact on the overall risk assessment see 2.10 and 2.12. It should also be noted that the rapporteur Member State has received the studies and summarised them in the addendum available after the experts´ meeting but they have not been peer reviewed. However, if the NOAELs proposed by the rapporteur Member State are agreed on this would imply that the ARfD and AOEL would be lowered (see 2.10).

2.8. Further studies

Metabolites

Dibutylamine is harmful (LD_{50} 205 mg/kg bw) by ingestion. An Ames test was provided, whose results were considered as positive. Data presented in the DAR indicates that dibutylamine showed a dose-related increase in mutation frequency in the TA1535 strain (-S9) in an Ames assay. It was noted that the Ames assay used DMSO as a vehicle, and the appropriateness of this when testing potential nitrosamines was questioned. The meeting concluded that the genotoxicity of dibutylamine had not been adequately addressed, and a new data requirement was set: a full *in vitro* data package is required.

The experts considered that data requirement for specific toxicological data on **carbofuran** was addressed in the carbofuran dossier.

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EFSA notes: Below, follows the summary on carbofuran and for further information, see the EFSA conclusion report for carbofuran.

Carbofuran is rapidly and completely absorbed and excreted in the rat. It is very toxic by ingestion (LD_{50} 7 mg/kg bw) and by inhalation (LC_{50} 0.05 mg/L) whereas toxicity during dermal exposure is moderate. Carbofuran is not a skin irritant or eye irritant or skin sensitizer but mortality was reported after exposure to eyes. The proposed classification is T^+, R28/R26 "Very toxic if swallowed and via inhalation", Xn, R21 "Harmful in contact with skin" and T, 39/41 "Danger of very serious irreversible effects" and Risk for serious damage to eyes". The critical target is inhibition of brain and RBC acetyl cholinesterase. The overall relevant oral short term NOAEL is 0.1 mg/kg bw/day based on the 1-year dog studies. It is genotoxic *in vitro* but negative in *in vivo* studies. The relevant long term NOAEL is 0.462 mg/kg bw/day from the rat study. Carbofuran induced decreased body weight in pups as well as pup survival. Furthermore, results from the open literature demonstrated that carbofuran caused testicular and spermatotoxicity in pups at dose levels of 0.4 mg/kg bw not associated with inducing general toxic effects. The classification of Reproduction Toxic Category 3, R62, is proposed. The metabolites 3-OH-carbofuran and 3-keto carbofuran are toxic (LD_{50} of 8 and 107 mg/kg bw, respectively), the hydroxy metabolite is genotoxic as well (Ames test). The acceptable daily intake (ADI) and acceptable operator exposure level (AOEL) is 0.001 mg/kg bw/day and the acute reference dose is 0.001 mg/kg bw with the safety factor of 100 applied should be regarded as provisional due to the concerns in relation to possible reproduction effects.

EFSA note: At the time of finalisation of this conclusion, at the EFSA Evaluation meeting in June 2006, it was noted that the new study on spermatogenesis in rats had been provided to the Rapporteur and also to ECB for consideration as part of the classification process (March, 2006).

EFSA confirmed that the study has been considered within the ECB process. In March 2006, the ECB classification meeting proposed that no classification for reproduction was required. EFSA understands from ECB that this conclusion was reached taking into account the results of the new study, which did not confirm the testicular and spermatotoxicity effects in rats reported in published papers. Thus, this position, reached within the ECB process, would support a confirmation of the reference values i.e. ADI, ARfD and AOEL that was provisionally agreed at EPCO 33 (Mammalian toxicology experts´ meeting), and a conclusion that no additional safety factor would be required. However it should be noted that the classification proposal has not been formally adopted by a vote within the ECB process nor have the results of the study been considered or peer reviewed within the risk assessment process under Directive 91/414/EEC.

Impurities

The meeting noted that *N*-nitrosodibutylamine exceeded the acceptable maximum concentration of 1 mg/kg (specified in the equivalence of technical materials document). The meeting noted that the structurally related *N*-nitrosodimethylamine was classified as very toxic, and that at concentrations of 0.001%-0.01% had the **risk phrase [R45] 'May cause cancer'**. The rapporteur Member State indicated that assuming *N*-nitrosodibutylamine was of comparable toxicity to *N*-nitrosodimethylamine, carbosulfan would be classified. Furthermore, IARC considered *N*-

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nitrosodibutylamine a category 2B carcinogen, and it was carcinogenic in all categories tested. It was noted that the level of *N*-nitrosodibutylamine in batches used in genotoxicity and carcinogenicity studies was not known, and a new data requirement was set for the notifier to provide this data.
EFSA notes: see 2.4.

For the impurity 5-chlorocarbofuran no toxicological data were submitted.

Human studies
In human volunteers, symptoms attributed to cholinesterase inhibition were seen at 0.25 mg/kg. Symptoms occurred in conjunction with a substantial reduction in red blood cell cholinesterase activity which was dose-related. The study has a limited scientific value due to the absence of important information (e.g. purity).

2.9. MEDICAL DATA

Symptoms of poisoning include excessive sweating, headache, chest tightness, weakness, giddiness, nausea, vomiting, stomach pain, salivation, blurred vision, slurred speech and muscle twitching. Paresthesia and mild skin reactions have also been reported. The applicant did not supply specific data for carbosulfan.

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

EFSA notes that the reference values reported below and agreed during the EPCO meeting should be regarded as provisional, due to the number of data gap identified during the process. The role of nitrosamines in determining health effects should be assessed with regard to their level in toxicological batches and their intrinsic properties have to be regarded as of concern, possibly leading to an increase of the safety factors applied. Also the missing acute and subchronic neurotoxicity studies might have an impact on some of the reference values, in particular AOEL and ARfD.
It should be noted that the rapporteur Member State, after the EPCO, submitted an addendum (Jan 06) proposing new values for AOEL and ARfD, according to the revision of a study and to a newly submitted study, respectively.

EPCO outcomes:
ADI
A NOAEL of 1 mg/kg bw/day from the 2-year rat study was identified as relevant based on eye toxicity and AChE inhibition; a safety factor of 100 was applied, to give an ADI of 0.01 mg/kg bw/day.

AOEL
On the basis of the data available, the systemic AOEL should be derived from a NOAEL of 2 mg/kg bw/day resulting from the 90-day feeding study in rats was agreed during the meeting. A safety factor of 100 was considered adequate. The meeting considered that no correction was necessary. The

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proposed systemic AOEL is 0.02 mg/kg bw/day. The meeting decided that the AOEL had to be confirmed upon receipt of other data (acute and repeated dose neurotoxicity data) from notifier.

ARfD

No acute neurotoxicity study in rats was provided. The 2-year study in rat was considered, applying a SF of 100. The ARfD is 0.01 mg/kg bw/day.

However, the meeting considered that an acute neurotoxicity study was often most appropriate for derivation of the ARfD. An acute and a repeated dose neurotoxicity study were submitted to the WHO by the applicant, and a new data requirement was set for these studies to be submitted. It was noted that the acute neurotoxicity study derived a NOAEL of 0.5 mg/kg bw (based on brain ChE effects), and the subchronic neurotoxicity study derived a NOAEL of 1.2 mg/kg bw/day, based on clinical signs and effects in FOB. As a result, the reference doses proposed by the rapporteur Member State were set as provisional reference doses, to be confirmed after evaluation of the neurotoxicity studies, which were requested to the applicant.

EFSA notes: Comments from rapporteur Member State after the experts´ meeting. In January 2006, the rapporteur Member State confirms the use of the NOAEL from the 90-day study in rats, but considering the new value of 1.2 mg/kg bw/day: the study in rats shows that 20 ppm corresponds to 1.2 mg/kg bw/d and not to 2 mg/kg bw/day as proposed in the original DAR. Therefore, the rapporteur Member State proposes a new AOEL of 0.01 mg/kg bw/day (SF 100). This approach has not been discussed nor peer reviewed by MSs.

For the ARfD, an acute neurotoxicity study in rats was provided in January 2006 and included in the addendum but not peer reviewed. The study was used as a basis for the ARfD in the JMPR assessment (2003); the relevant NOAEL form this study is 0.5 mg/kg bw. A new ARfD = 0.005 mg/kg bw was proposed by the rapporteur Member State (SF 100). The JMPR agreed on an ARfD of 0.02 (SF 25).

2.11. Dermal absorption

No studies were submitted. A default dermal absorption value of 100% was confirmed for Marshal 10G during the meeting based on physico-chemical properties. The meeting noted that the notifier did not support Marshal 25 CS at EU level any longer.

2.12. Exposure to operators, workers and bystanders

EFSA note: The risk assessment for operators has to be regarded as inconclusive due to data gaps and the provisional AOEL (see 2.4, 2.5, 2.8 and 2.10). The estimated operator exposure presented below, for sake of transparency, is based on the provisional AOEL.

Operator exposure

Marshal 10G is a granular formulation: an operator exposure estimate using the PHED model was provided by the applicant as the UK-POEM and German Model are not applicable to assess exposure to such a type of formulation.

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PHED

When Marshal 10G is applied using tractor-mounted/drawn equipment it is estimated that the total systemic operator exposure to carbosulfan is 20% of the provisional AOEL of 0.02 mg/kg bw/day (considering 15 ha/day treated area, gloves and a respirator worn during mixing/loading and application). When gloves only are worn, operator exposure is 36% of the provisional AOEL of 0.02 mg/kg bw/day.

UK POEM - BBA

An estimation of operator exposure was also performed by the rapporteur Member State with the German and POEM model using the tractor mounted hydraulic boom and nozzles model (UK POEM) and the tractor field crops (BBA model) taking into account that the use of granular applicators distributing the granules by drilling reduces operator exposure to loading since no water is needed and eliminates mixing phase as well as application exposure. In these conditions, operator exposure exceeds the provisional AOEL of 0.02 mg/kg bw/day.

Bystander exposure

Marshal 10G:

No established models are available to estimate the level of bystander exposure likely to arise during granule application. It can be assumed that bystanders may be present during the field use of Marshal 10G. The applicant considered that bystander exposure to vapour or airborne particles at the time of application is likely to be negligible. This was agreed by the rapporteur Member State.

The meeting asked the rapporteur Member State to present the estimated bystander exposure in an addendum with revised values. So far, an addendum has not been submitted.

Worker exposure

As Marshal 10G is applied to the soil at the time of planting/transplanting and incorporated, workers entering treated are not likely to be exposed to dislodgeable foliar residues of carbosulfan.

3. Residues

Carbosulfan was discussed in the experts' meeting for residues in September 2005 (EPCO 34). It is noted that the addendum of September 2005 was distributed during the discussion of carbosulfan in EPCO 34. The experts tried to consider the information in the addendum as good as possible. However due to the very late submission a detailed consideration of the presented information was not possible. Therefore, the addendum of September 2005 should not be considered as peer reviewed.

The initially proposed representative uses for inclusion of carbosulfan in Annex I of 91/414/EEC were an in-furrow granular application to maize and sugar beet and a foliar spray application to citrus and cotton. The uses involving a foliar spray application were withdrawn by the applicant during the EU review process (i.e. not further supported with respect to Annex I inclusion). Therefore the peer review for these uses stopped after the first evaluation meeting, however for the sake of transparency the evaluation of residue data related to these uses are presented below as far as possible.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

Metabolism of carbosulfan was studied in sugar beet, soybean, maize and rice plants following a soil application; in oranges, alfalfa and sugar beet following a foliar treatment and in rice following a direct treatment of the ear heads with carbosulfan. In the studies material radio-labelled at either the phenly-ring or the dibutylamine-group was used. Based on the available studies the metabolic pathway of carbosulfan in plants can be considered as sufficiently investigated.
In all cases, metabolism of carbosulfan was initiated by the cleavage of the S-N bond into carbofuran and dibutylamine. Carbofuran was further metabolised by subsequent hydroxylation on the furane ring to 3-OH-carbofuran. Numerous other metabolites were generated from carbofuran by successive hydroxylation or hydrolysis and oxidation steps, amongst them 3-keto-carbofuran and phenol derivates of carbofuran such as carbofuran-7-phenol[6], 3-hydroxy-7-phenol[7] and 3-keto-7-phenol[8], (phenol metabolites hereafter) which were further conjugated. Dibutylamine was slowly degraded to minor levels of mostly unidentified products; however, the dibutylamine derivates N-formyldibutyl amine and acetyl-dibutylamine were identified in plant material.

With the exception of sugar beet, carbosulfan, carbofuran and 3-OH-carbofuran (together *ca* 30-80% TRR) and dibutylamine (40-60% TRR) were found to be the major components of the total residue in plants having received a direct treatment (oranges, alfalfa, rice) at sampling times between 15 to 45 days after application. In sugar beet leaves, however, at comparable sampling times 3-OH-carbofuran, 3-hydroxy-7-phenol and 3-keto-7-phenol were major compounds, accounting for up to *ca* 17%, 14% and 23% of the total residue, respectively, whereas the level of carbosulfan and carbofuran was minor (together < 3% TRR). Dibutylamine (up to 47% in leaves) and N-formyl-dibutylamine (up to 31% in leaves and 12% in roots) made up a major part of the residue in sugar beet treated with carbosulfan labelled at the dibutylamine -group. No metabolite identification was performed in the roots of plants treated with the phenyl-ring labelled carbosulfan.
In crops grown following a soil application of carbosulfan the metabolic pattern was similar as in directly treated crops, with the exception, that carbosulfan was hardly detected in these crops. Carbofuran and 3-OH carbofuran made up the majority of the total residue with their ratio depending on the sampling time, and were predominant primarily at early sampling stages. With time, the level of phenol-compounds increased, and besides 3-OH carbofuran the phenol metabolites appeared to be predominant metabolites identified in the mature crops (maize, soybean). Dibutylamine was as well a major metabolite found in crops grown following a soil treatment (immature maize and rice plants, silage, stalks and leaves at harvest). Dibutylamine was present up to 30% TRR and was only slowly decreasing with time. Very few data are available on the occurrence of dibutylamine in edible plant

[6] carbofuran-7-phenol: 2,3 dihydro-2,2-dimethyl-7-benzofuranol
[7] 3-hydroxy-7-phenol: 2,3-dihydro-2,2-dimethyl-3,7-benzofurandiol
[8] 3-keto-7-phenol: 2,3-dihydro-2,2-dimethyl-3-oxo-7-benzofuranol

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parts. Dibutylamine wasn't analysed for in the mature roots, grains and seeds in the metabolism studies with soil treatment.

Dibutylamine is still under discussion concerning its potential genotoxicity (see 2.8) Even though dibutylamine is not specific to carbosulfan metabolism it is a predominant residue of carbosulfan metabolism with a potential toxicological relevance. The rapporteur Member State raised a concern that dibutylamine might be also a precursor of *N*-nitrosodibutylamine, a category 2B carcinogen, however data underpinning this assumption has not been available.
Carbofuran, another main carbosulfan metabolite, is an active substance itself. It has a higher toxicity than carbosulfan. Also 3-OH-carbofuran and 3-keto-carbofuran are of higher toxicity than carbosulfan. The phenol metabolites were tested regarding their acute toxicity and considered of lower toxicity than carbosulfan, carbofuran and 3-OH-carbofuran. (Refer to 2.8 and to EFSA conclusion on carbofuran)

The experts' meeting for residues EPCO 34 agreed on the need to further evaluate the dibutylamine residues in plant matrices and to consider dibutylamine as a component to be included in the residue definitions for risk assessment. The rapporteur Member State proposal in the addendum of February 2006, not to include dibutylamine in the plant residue definition for risk assessment, was neither peer reviewed nor discussed by experts. EFSA notes that in crops with foliar treatment (oranges and in alfalfa) dibutylamine was a major residue at harvest. Due to the limitation of the available data on dibutylamine in the edible parts of soil applied crops it is difficult to say whether or not dibutylamine would be also present in these plant parts. It could be assumed from the data on non-edible plant parts of those crops that dibutylamine residues, if present, might be in the same order of magnitude as carbofuran residues.

It can be concluded that the qualitative metabolic pattern observed in plants treated with carbosulfan was independent from the mode of application whereas significant quantitative differences were noted, mainly with regard to the rate (percentage) of carbosulfan found in the crops. In terms of the representative uses with foliar application some aspects on applicability of the submitted metabolism studies still need to be clarified at MS level if foliar uses are reinstated in the future. (Refer to evaluation table open points 3.3 and 3.5)
Considering the rate of occurrence and the toxicological relevance of carbosulfan and some of its metabolites it is proposed to define the residue for risk assessment purposes as carbosulfan, carbofuran and 3-OH carbofuran. Particular consideration should be given to dibutylamine. In case dibutylamine will be considered as toxicological relevant the residue definition has to be reconsidered and residue trials data will need to be reassessed in the light of that information.
Due to the fact that carbofuran is used as a pesticide itself, for monitoring a residue definition consisting of two parts was considered necessary to propose: 1) Carbosulfan to be monitored separately from 2) Carbofuran defined as sum of carbofuran and 3-OH-carbofuran expressed as carbofuran equivalents. In accordance separate MRLs for carbosulfan and carbofuran have been proposed resulting from the uses of carbosulfan in crops. (see 3.4) Whether or not there is a need to

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also monitor residues of dibutylamine will need to be reassessed upon receipt and evaluation of the required toxicological data.

Residue trial data under field conditions have been submitted on cotton and citrus from Southern Europe and on maize and sugar beet from both European regions. Carbosulfan, carbofuran and 3-OH-carbofuran are the residues determined with a LOQ of 0.05 mg/kg per compound. It is noted that for the uses with foliar application i.e. cotton seed and citrus the data set of trials is incomplete and further data will be needed if foliar uses are reinstated in the future. Despite the submission of one further trial for the representative use in maize EPCO 34 concluded that the data base of residues trials in accordance with the cGAP is still incomplete and permits only a provisional assessment. After the meeting the rapporteur Member State indicated its disagreement with the EPCO 34 decision and considers the requirement of further residue trials is not necessary. Available trial data indicate residues being below the respective LOQ for all analytes in maize kernels, whereas in whole plants with cobs residues of carbofuran and 3-OH-carbofuran up to 0.14 mg/kg were determined.
In sugar beets a complete data set was submitted for N-EU and limited data have been available for S-EU. Even though residues in roots were mainly below the respective LOQ, residues might reach or exceed the LOQ. EPCO 34 considered that it was a ‘low residue’ situation as opposed to a ‘no residue’ situation in sugar beet. The potential residues in the root could not be discounted. The uptake of residues into sugar beet was supported by positive results found in carbosulfan residue trials with a higher application rate than the proposed rate for the representative use. It is noted that the rapporteur Member State does not agree with the EPCO 34 conclusion and considers the residue situation in the sugar beet is a ‘no residue situation’.
EPCO 34 felt that for further considerations it would be necessary to check the validity of, and that the minimum number of trials is presented to support the proposed uses. Furthermore, it could not be concluded whether the residue trials are supported by sufficient storage stability data that cover all components included in the residue definition (data only available for orange matrices).

The investigation of effects of industrial or household processing on the nature of the residue was triggered for the representative use on citrus (not further supported with respect to Annex I inclusion). A position paper of the applicant for non-submission of those data was assessed by the rapporteur Member State in the addendum of February 2006 and was therefore not peer reviewed nor discussed by experts.
In a citrus processing study, the effects on the level of carbosulfan, carbofuran and 3-OH- carbofuran in processed citrus products were investigated. The data indicate high concentration of carbosulfan and carbofuran in citrus oil and of 3-OH-carbofuran in dried pulp, whereas no residues about the respective LOQ (0.05 mg/kg) were found in citrus juice. Whether other degradation products or metabolites were present at significant levels was not investigated.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Since carbosulfan is degraded very rapidly in soil, the rapporteur Member State considered studies in succeeding crops or a waiting period for planting succeeding crops are not necessary. However, also

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in soil carbosulfan is largely degraded to the more toxic carbofuran and to dibutylamine. Carbofuran appears more persistent in soil than carbosulfan and no degradation parameters are available for dibutylamine (refer to 4.1). Thus the experts' meeting for residues agreed that there is a need to address residues in succeeding crops following the application of carbosulfan to primary crops. It is noted that the rapporteur Member State does not agree with the experts' meeting decision. However, EFSA still supports the EPCO 34 decision.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Livestock animal metabolism was studied in lactating goats and laying hens orally dosed with carbosulfan radio labelled at either the phenyl-ring or the dibutylamine group.
Carbosulfan was rapidly metabolised and excreted by livestock animals. Numerous metabolites identified in the animal tissue, organs, eggs and milk, respectively, are reflecting the existence of multiple degradation pathways in the animal body. Based on the radioactivity characterised in animal matrices it was concluded that the degradation of carbosulfan in livestock animals proceeds via the following pathways: Hydrolytic cleavage of the N-S bond of carbosulfan into carbofuran and dibutylamine with subsequent oxidation of the methyl group of the carbamate or of the methyl group of the furane ring and hydrolysis of the carbamate moiety followed by further oxidations. The phenyl portion of the molecule was converted into the carbamate and phenolic derivatives, while the dibutylamine moiety was oxidized into compounds containing the amine fragment and incorporated into natural products such as fatty acids, triglycerides, carbohydrates and proteins. Many metabolites were present as conjugated compounds (lipid or amino acids conjugates).
All the metabolites identified in livestock animals have been found in the rat metabolism. Even though the relevant residues on potential feeding stuff are besides carbosulfan also carbofuran and 3-OH- carbofuran (and possibly dibutylamine), the available metabolism studies can be considered appropriate, since the referred to metabolites are generated in livestock animals, too.

Levels of recovered radioactivity in animal matrices strongly depended on the administered label. In tissues and organs of animals dosed with phenyl-labelled carbosulfan radioactive residues were highest in liver of poultry and goat, in goat kidney and in poultry muscle and skin. In matrices of animals dosed with dibutylamine-labelled carbosulfan highest residue levels were found in goat fat and in egg yolk followed by the liver of both species. The significant higher residues of the dibutylamine-label found in fatty matrices could be explained by the cleavage of the fat soluble dibutylamine side chain of carbosulfan.
Characterisation and identification of radioactivity was carried out depending on the level of the recovered total residues in only some of the edible matrices. Carbosulfan per se was, if detected at all, only present at very low levels (less than 2% TRR). 3-OH-carbofuran presented a major part of the residue in poultry muscle (37% TRR) and goat milk (up to 34% TRR) and kidney (22%TRR) whereas carbofuran residues were always below 10% TRR in all analysed matrices. Dibutylamine was the predominant metabolite in poultry muscle (22% TRR) and liver (37% TRR). In poultry fat and eggs only *ca* 4%TRR was identified as dibutylamine, whereas more than 85% TRR in these matrices remained unidentified. In goat matrices dibutylamine was either not radio-detected or found

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at very low levels. However, characterization of the radioactivity in fat showed that 82% of the TRR were recovered as fatty acids and a non negligible fraction of radioactivity was characterised as non conjugated and conjugated amines susceptible to contain the metabolite dibutylamine

The experts meeting for residues EPCO 34 agreed on the need to propose a residue definition for livestock animals. Based on the data and knowledge available at the time of the meeting EPCO 34 proposed to provisionally define the relevant residues in animal products as 3-OH-carbofuran. However the experts agreed on the need to further evaluate livestock animal data, in particular unidentified residue in fat and the dibutylamine residues in animal matrices, and to consider dibutylamine as a component to be included in the residue definitions for risk assessment. In the addendum of February 2006 the rapporteur Member State partially addressed the EPCO 34 request, however the provided evaluation was neither peer reviewed nor discussed in an experts' meeting and should not be considered as agreed.
In terms of the representative uses, relevant feed items are sugar beet roots and leaves, maize and –if use in citrus will be reinstated in future– citrus pomace. The dietary burden of livestock animals from relevant residues (i.e. carbosulfan, carbofuran, 3-OH-carbofuran and potentially dibutylamine) in those plant parts or plant products needs to be estimated to conclude on whether or not significant residues may occur in edible animal matrices and also whether feeding studies are required. Due to the lack of peer reviewed evaluation of relevant data and information it is not possible to conclude the issue at this stage.

3.3. CONSUMER RISK ASSESSMENT

With the current knowledge and data available, and with the provisionally agreed toxicological reference values for carbofuran, which are applied also to 3-OH-carbofuran and the provisionally agreed toxicological reference values for carbosulfan it is not possible to provide a reliable assessment of consumer risk. A conclusion on whether or not dibutylamine is also relevant in the consumer risk assessment could not be reached during the evaluation process.

It is noted that following the experts' discussion and decisions, no updated chronic risk assessment was submitted by the rapporteur Member State in an addendum (open point 3.13) and the revised acute risk assessment provided in the addendum of September 2005 is not peer reviewed. The initially presented risk assessment by the rapporteur Member State is summarised below (presented in italic) for the sake of transparency, but should not be considered as agreed. To assess consumer risk the rapporteur Member State followed the approach of a separated intake assessment of carbosulfan on one hand and the sum of carbofuran and 3-OH-carbofuran residues on the other hand. The initially proposed provisional MRLs and supervised trials medium residue data (STMR), including the ones for foliar uses no longer supported, were applied in the calculations.

In the chronic exposure assessment the TMDI was estimated based on the FAO/WHO GEMS/Food European Diet, the German diet (4-6 yrs female child) and the UK PSD consumer exposure model.

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The estimated dietary intake of carbosulfan per se was in those calculations significantly below (<10%) the provisionally allocated carbosulfan ADI of 0.01 mg/kg bw/day for all considered consumer groups. The estimated dietary intake of the carbosulfan metabolites carbofuran / 3-OH-carbofuran, however, ranges from 36% to 693% of the provisionally allocated ADI for carbofuran of 0.001 mg/kg bw/day. In a refined assessment the NEDI of carbofuran / 3-OH-carbofuran residues was calculated based on UK PSD consumer exposure model, supervised trials medium residue data (STMR) and processing factors. In these estimates the intake of carbofuran / 3-OH-carbofuran ranges from 25% to 93% of the carbofuran ADI.

The acute dietary intake of carbosulfan per se reached 5% of the provisionally allocated carbosulfan ARfD of 0.01 mg/kg bw/day in the case of toddlers consuming maize and 40% ARfD for toddlers consuming oranges. In acute intake estimates of carbofuran and 3-OH-carbofuran presented in the DAR 81% of carbofuran ARfD was reached by the consumption of sugar beet, 102 % ARfD by the consumption of maize and up to 3000% ARfD by the consumption of citrus fruits by toddlers (UK consumption data).

Potential residues in food of animal origin and/or rotational crops could not be considered in the estimates above due to lacking data or lacking peer reviewed evaluation of data. Following the EPCO 34 discussion some of the input parameters applied in the intake estimates as variability factors, MRL or STMR derived from the available residue data might need to be reconsidered in the light of the EPCO discussions.

Moreover, EFSA notes that the approach of a separated intake assessment for carbosulfan and carbofuran/ 3-OH-carbofuran residues, as applied by the rapporteur Member State in the DAR, ought to be discussed in general, since a separated assessment does not cover the worst case exposure for the consumer. All three compounds have proven in metabolism studies to be simultaneously present as residues on food/feed items. Furthermore, available residues trials, in particular for foliar uses, indicate that depending on the GAP there is a possibility of simultaneous exposure of consumers to all three relevant compounds.

In acute toxicity studies all three compounds showed the same mode of action and toxicological endpoint, i.e. cholinesterase inhibition, whereas only the potency of the observed effect was different. As the consumer might be exposed to a combination of all three relevant compounds the acute consumer risk to the sum of all three compounds should be assessed by either using the lowest allocated ARfD as a worst case approach or by converting to the level of the individual compounds to a common residue before summation. In the latter case a comprehensive data base of residue decline studies in the respective crops will be needed in order to get a better picture on the decline curves as well as the corresponding magnitudes of the individual compounds over the time to permit the determination of the worst case situation for the consumer.

The chronic consumer risk might be assessed in the same manner, even though it is noted that no adequate chronic toxicological data is currently available for 3-OH-carbofuran. The metabolite 3-OH-carbofuran is assumed to be of comparable toxicity as carbofuran based on acute toxicity studies only.

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3.4. PROPOSED MRLS

The currently available data allow only provisional MRLs proposals as the data base for all representative uses is incomplete. Moreover it might need to be reviewed whether the proposed MRL for sugar beet at LOQ level is sufficiently high to cover anticipated residues in that crop (refer to 3.1.1).
Separate MRLs for carbosulfan and carbofuran have been proposed resulting from the uses of carbosulfan in maize and sugar beets

Carbosulfan 0.05 * mg/kg
Carbofuran (sum of carbofuran and 3-OH-carbofuran expressed as carbofuran) 0.1 * mg/kg

The initially proposed MRLs for the uses on citrus and cotton no longer supported for Annex I inclusion of carbosulfan are not presented, since the evaluation of that uses was stopped after the first evaluation meeting.

4. Environmental fate and behaviour

Carbosulfan fate and behaviour into the environment was discussed in the meeting of MS experts EPCO 31 (September 2005) on the basis of DAR (July 2004), the carbosulfan Reporting and Evaluation tables and the updated List of End Points (August 2005). An addendum to the fate and behaviour chapter has been provided on 18 May 2006. When reported, the information in the addendum has been summarized too briefly to draw any conclusion on its reliability. Studies or reports presumably submitted by the applicant are not adequately referenced. Therefore, studies submitted by the applicant after the DAR was submitted are considered neither evaluated nor peer-reviewed in this conclusion.

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

The route of degradation of carbosulfan was investigated under dark aerobic conditions at 20 ºC and 40 % MWHC in one study (Baumann 2002) with four soils (pH 5.8 – 7.3; OC 0.78 – 3.89 %; clay 8.2 – 23.3 %) and ^{14}C-phenyl labelled carbosulfan as test substance. In this study, only **carbofuran** (max. 48.7 % AR after 7 d) was found as a major transformation product of carbosulfan in soil. Several minor metabolites were identified being 3-keto-carbofuran (max. 5.3 % AR after 14 d) among them. The meeting of MS experts considered that this metabolite needs to be further assessed because it contains the active carbamate moiety. Although the side chain was not labelled, amounts of dibutylamine (max. 5.4 % of the initial molar amount) were also quantified in these experiments. The mineralization was very limited (max CO_2 2.3 % AR) and bounded residues increased up to maximum of 90 % AR after 100d.
In a separated study (Markle 1981a) aerobic (for 28 d) and anaerobic degradation of ^{14}C-phenyl labelled carbosulfan is compared in two soils (pH 6.1 – 7.0; OC 2.96 – 4.58 %; clay 25 %) incubated

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at 22 ºC and 60 % of MWHC. In this study maximum level of carbofuran formed was 69.3 % AR after 7 d and **3-keto-carbofuran** reached levels of 6.6 % AR after 28 d (end of the aerobic study). An analogous study (Markle 1981b, same soils and experimental conditions) was performed with ^{14}C-dibutylamine labelled carbosulfan. **Dibutylamine** (max 21.5 % AR after 3 d) was found as a major aerobic soil metabolite in these experiments. The anaerobic part of these studies was not considered acceptable by the rapporteur Member State.

No valid degradation study of carbosulfan in soil under anaerobic conditions is available. Also photolysis in soil was not investigated. Two soil photolysis studies are available for the main metabolite carbofuran in the corresponding DAR. On basis of these studies, carbofuran has been considered stable to photolysis in soil.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Rate of degradation of carbosulfan in soil under dark aerobic conditions was calculated in the same studies provided to investigate the route of degradation. However, data from not acceptable studies are taken into account the table B.8.1.2.1-1 of the DAR were the half lives are summarized and the mean calculated. It is emphasized that only studies by Baumann (2002) and Markle (1981a, 1981b) were considered of sufficient quality to be used in the risk assessment.

Evaluation meeting agreed that a re-evaluation of the degradation kinetic in degradation studies, including assessment of the goodness of fit, needs to be performed by the applicant. Reassessment was provided to the rapporteur Member State in June 2005 but has still not been assessed and peer reviewed. Therefore, it has not been possible to agree during the Peer Review on the laboratory degradation end points for carbosulfan.

In a separated non radio labelled study, rate of degradation of carbosulfan was also measured under dark aerobic conditions in one soil (pH 7.1, OC 3.89 %, clay 16.5 %) at 10 ºC and 40 % MWHC. Under these conditions a half life of 25.4 d was obtained (as reported in table B.8.1.2.1-1).[9] Summaries of some field dissipation studies performed with carbosulfan in EU are available. Half life of carbosulfan in these trials ranges between 0.35 to 31.3 d. Half life of metabolite carbofuran in the these trials ranges between 1.3 to 71.9 d. EFSA notes that in the context of the carbofuran discussion, the meeting of MS experts was not able to determine the reliability of these studies. A position paper from the applicants is available (June 2005) but has still not been assessed and peer reviewed. Also some summaries of field studies performed in USA are available in the dossier. The meeting of MS experts agreed that to assess these studies with respect to EU conditions more background information would be needed.

PEC in soil were calculated in the DAR for carbosulfan and carbofuran based on the field worst case half lives (DT_{50} carbosulfan = 35 d, DT_{50} carbofuran = 71.9 d) and the representative uses in maize and sugar beet (Marshal 10G) and citrus and cotton (Marshal 25 CS).

No degradation parameters are available for soil metabolite dibutylamine. Evaluation meeting agreed that half life of dibutylamine in soil and PEC soil for this metabolite need to be determined. A

[9] A different value is given in the study summary within main text of the DAR. The rapporteur Member State confirmed that the right value is 25.4 d.

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position paper was provided by the applicant in June 2005 but has still not been evaluated and peer reviewed.

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

A batch adsorption / desorption study was performed with carbosulfan and its metabolites carbofuran and dibutylamine in four soils. In this study carbosulfan shows to be slight to low mobile in soil, carbofuran very high mobile and dibutylamine medium to high mobile in soil. The rapporteur Member State concluded in the DAR that this study is of limited quality. The meeting of MS experts agreed that the study was not valid due to serious methodological flaws and therefore identified a data gap for a valid adsorption study for carbosulfan and dibutylamine. For the metabolite carbofuran an additional study (from a different notifier Dianica; Mamouni, 2002) is available in the dossier of carbofuran as active substance.
A soil TLC study and two aged soil column leaching studies of limited quality are available.
A lysimeter study performed with two lysimeters in loamy sand soil is available. Carbosulfan was applied to bare soil at rate equivalent to 1.05 Kg a.s. / ha. The average concentration in the leachate for the two years that lasted the experiments was 0.82 – 0.85 μg carbosulfan equivalents / L leachate. However, annual average concentrations and detailed characterization of the residue is missing in this study. Evaluation meeting agreed that the levels of soil metabolite dibutylamine need to be determined in the lysimeter leachate samples and that the two new lysimeters performed with carbofuran (carbosulfan metabolite) should be submitted and assessed. These studies were submitted by the applicant in June 2005 but still have not been evaluated and peer reviewed. For dibutylamine a position paper was provided by the applicant in June 2005 but has still not been evaluated and peer reviewed.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Degradation of carbosulfan in sterile buffer solutions at 25 ºC is pH dependent. Carbosulfan hydrolyses with half lives lower than 1 d at pH 5 and 7 and with a half life of 7 d at pH 9. Main hydrolysis products are carbofuran and dibutylamine. Carbofuran subsequently degrades to carbofuran-7-phenol.
Photolysis in water had not been investigated for carbosulfan in the original dossier. A data gap was already identified in the physical and chemical properties section of the DAR. The study was provided by the applicant and evaluated by the rapporteur Member State in the addendum to section B.2 of the DAR (September 2005). This study shows that photolysis may contribute to the environmental degradation of carbosulfan. Hydrolysis metabolite carbofuran-7-phenol is also found to be the major metabolite in the irradiated samples of this study (16.7 % AR after 23.9 h). Two regions of polar degradation products (amounting to 66.7 % AR) were found but not characterized. The environmental relevance of these metabolites is uncertain and was not peer reviewed by the

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meeting of MS experts since the study was still not evaluated at the time the fate and behaviour in the environment meeting took place.

Carbosulfan is not readily biodegradable according the available study.

Dissipation in water / sediment was investigated in one study with two dark aerobic water sediment systems ($pH_{sediment}$ 6.8 – 6.9; pH_{water} = 7 – 8.5) at 20 ºC and 10 ºC and at two different levels (0.2 and 0.4 mg a.s / unit).

Carbosulfan was low persistent in all experiments performed ($DT_{50\ whole\ system\ 20\ ºC}$ = 4.2 – 5.4 d; $DT_{50\ whole\ system\ 10\ ºC}$ = 10 d). Main metabolites formed were carbofuran (max. 34.7 % AR in water; max. 20.1 % AR in sediment) and carbofuran-7-phenol (max. 11.6 % AR in water; max. 3.21 % AR in sediment). A non characterized metabolite (Unknown 3) also appears at levels above 10 % AR in the sediment of some systems (max. 20.11 % AR after 7 d). This compound consisted in a single well defined chromatographic peak. The amount of bound residues increased steadily up to 30.5 – 43.0 % AR at the end of the experiments (102 d).

A separated study was performed to obtain higher amounts of Unkown 3 for its identification. The study was unsuccessful and only a tentative structure was proposed based on the mass spectrometry of the samples in the original study. This tentative structure contains the carbamate moiety and may be expected to produce carbofuran when degraded.

No half lives are reported in carbosulfan DAR for metabolites carbofuran and carbofuran-7-phenol in the water sediment systems.

Applicant provided aerobic and anaerobic water sediment studies for the metabolite carbofuran that have not been summarized in the DAR. Evaluation meeting agreed that an addendum need to be produced to summarize the carbofuran studies used in the assessment of carbosulfan. The addendum is still awaited, however EFSA may confirm that these are the same studies presented by applicant FMC in the carbofuran dossier and summarized by the rapporteur Member State in the carbofuran DAR. The aerobic carbofuran water sediment study (FMC, Saxena A.M., Marengo, J. R., 1994) was performed on a dark aerobic system with pond sediment (pH 5.3) and water (pH 6.1) at 25 ºC during 30 d. Carbofuran dissipates from the surface water by degradation and partition to the sediment. The carbofuran degraded in the whole system with a first order half life of approximately 41 d. Transformation products 3-OH-carbofuran and 3-keto-carbofuran were found both in the water and the sediment phase at low levels (< 0.3 % AR). Mineralization was low (CO_2 = 1.81 % AR at the end of the study) and bound residue reached a maximum of level of 32.8 % AR. The rapporteur Member State required in the DAR a new water/sediment study or additional information on 7-phenol metabolite and on the degradation rate of carbofuran. EFSA recalculated the half life ($DT_{50\ whole\ system}$ = 44.6 d) by non-linear regression that passed the χ^2 test with an error level of 6.8 %. Fitting is not very good and it would be necessary to have more data points at longer times to have a reliable half life. However, the available data clearly indicate that a half life must be longer that 30 d for this system. Available water sediment studies under alkaline conditions (from carbofuran applicant Dianica) show the faster degradation of carbofuran and the formation of carbofuran-7-phenol at high levels under these conditions.

$PEC_{SW/SED}$ were calculated by the applicant based on an *ad hoc* modelling exercise. Spray drift (Marshal 25 CS), drainage, run-off and erosion (Marshal 10G and Marshal 25 CS) are potential routes

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of exposure of surface water. However, none of these modelling exercises follows FOCUS SW scheme. Since the input parameters selected to calculate PEC_{SW} and the assumptions made were not fully justified, the rapporteur Member State considered that more appropriate PEC_{SW} calculations were necessary to finalize the assessment of the EU representative uses and proposed the use of FOCUS SW scheme. No PEC_{SW} were proposed for dibutylamine. Evaluation Meeting confirmed the rapporteur Member State data requirement for FOCUS SW $PEC_{SW/SED}$ and agreed that PEC_{SW} for dibutylamine need to be calculated. FOCUS SW calculations and a position paper for dibutylamine were provided by the applicant in June 2005 but have still not been evaluated and peer reviewed.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The applicant presented an estimation of the potential for ground water contamination based on the FOCUS GW scheme (PRZM). The 80^{th} percentile of the annual average concentration in the leachate at 1m depth was calculated for the MARSHAL 10 G and MARSHALL 25CS representative uses. For carbosulfan concentrations calculated were below 1 ng / L. The rapporteur Member State considered that half life and K_{oc} employed for carbofuran in the calculation were not justified and proposed a data requirement for new PEC_{GW}. This data requirement was confirmed by the Evaluation Meeting that additionally required calculation of PEC_{GW} for metabolite dibutylamine. New FOCUS GW calculations for carbofuran and a position paper for dibutylamine were provided by the applicant in June 2005 but have still not been evaluated and peer reviewed. Additionally, experts meeting indicated that potential ground water contamination by soil metabolite 3-keto-carbofuran should be addressed. This is a new data gap identified by the meeting of experts.

4.3. FATE AND BEHAVIOUR IN AIR

Volatilization studies from soil and plant surface are available in the carbosulfan dossier. These studies are not properly summarized in the carbosulfan DAR but the rapporteur Member State considers they show that carbosulfan will not pose a risk to the atmosphere.
Carbosulfan is not a volatile compound. Atmospheric half life for photochemical oxidations has been calculated as 2 h. It is not expected that carbosulfan may contaminate the air compartment or be prone to long range transport through air.
Carbosulfan transform in the active substance carbofuran. No data on the fate in air of carbofuran is available in the carbosulfan dossier. Data in carbofuran dossier shows that contamination of the air compartment and long range transport thought air is not expected for carbofuran.

5. Ecotoxicology

Carbosulfan was discussed at the EPCO experts' meeting for ecotoxicology (EPCO 32) in September 2005. The discussion focused on confirming the data requirements originally proposed by the rapporteur Member State and on identifying additional data gaps for the proposed representative uses, since no additional information or studies provided had been evaluated by the rapporteur Member

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State. No summaries of studies on the metabolite carbofuran were included in the DAR. All toxicity values for the metabolite carbofuran in the DAR on carbosulfan and in this report are from the DAR on carbofuran.

5.1. Risk to terrestrial vertebrates

Acute, short-term dietary and reproductive toxicity studies are available to assess the risk from carbosulfan. An acute bird study with the formulation MARCHAL 25 CS is also available that indicates that this formulation might be somewhat more toxic than what is expected from the content of the active substance. No study with the granular formulation was available in the DAR.

The proposed representative uses of carbosulfan are as insecticide with foliar application of the product MARCHAL 25 CS in cotton and citrus, and application of the granular formulation MARCHAL 10 G in maize and sugar beet.

The first tier risk from the use of MARSHAL 25 CS to generic species, representing insectivorous birds in citrus and cotton, medium herbivorous birds in cotton and small herbivorous mammals in citrus, was assessed according to the SANCO/ 4145/2000. All TER values are below the relevant Annex VI trigger indicating a potential risk.

For the granule formulation the acute LD_{50}, the acute NOEL, the dietary LC_{50} and the $NOEL_{reproduction}$ were recalculated in number of granules for different sizes of birds and mammals. The numbers of granules that have to be ingested by a bird to reach the LD_{50} or LC_{50} are low, especially for small birds (11 and 4 respectively). Wildlife observations in one field treated with MARSHAL 10 G are available. However the information was considered of limited value by the rapporteur Member State. The number of granules that have to be ingested by a mammal to reach the LD_{50} is 30.5. Granules are not attractive to mammals and the acute risk can therefore be considered as low. To reach the NOAEL for mammals 1, 2 and 9 granules have to be ingested by a 10 g, 25 g and 100 g mammal respectively. The experts' meeting agreed that the risk has to be further addressed. Also the risk from ingestion of treated seedlings needs to be further addressed for both birds and mammals. The applicant proposed to use a residue value of 0.1 mg/kg based on a metabolism study in maize. However actual carbofuran concentrations of 2.79 mg/kg measured in maize after 31 days indicate that the concentration in seedlings could be higher.

No assessment of the risk from secondary poisoning or from exposure to contaminated drinking water was presented in the DAR. The risk to birds and mammals from consumption of contaminated earthworms was assessed by the rapporteur Member State and presented in an addendum of May 2006 but has not been peer reviewed.

Additional data and refined assessments are needed in order to conclude on the risk to birds and mammals from both evaluated representative uses. The reader is referred to the "List of studies to be generated, still ongoing or available but not peer reviewed" for details.

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5.2. Risk to aquatic organisms

Based on the available acute toxicity data, carbosulfan is classified as very toxic to aquatic organisms, with an EC_{50} of 0.0015 mg/L for *Daphnia magna* the most sensitive species tested. Also the metabolite carbofuran is very toxic to aquatic organisms with the lowest acute toxicity value obtained for *Gammarus fasciatus* with a LC_{50} of 0.0028 mg/L.

The first tier TER values for carbosulfan were calculated based on PEC_{sw} from spray drift for the use of MARCHAL 25 CS in cotton and citrus. TER values for carbofuran were calculated considering drainage as route of entry. In the case of the granular formulation MARCHAL 10 G for use in maize and sugar beet, only carbofuran is expected to reach surface water. Based on available PEC_{sw} values from spray drift, risk mitigation measures comparable to more than 50 m buffer zones would be needed to meet the Annex VI acute trigger for invertebrates in both cotton and citrus and for fish in citrus. Based on available PEC_{sw} for the use in maize and sugar beet a first tier long-term risk was identified for invertebrates from exposure to carbofuran. It was however agreed in the experts' meeting that for MARCHAL 10 G a revised assessment based on PEC_{sw} from FOCUS modelling should be provided. It should be noted that also for the use of MARCHAL 25 CS drainage and runoff events are likely to contribute to contamination of surface water with carbofuran. The EFSA proposes that the assessments for all uses are reconsidered using PEC_{sw} from FOCUS modelling (see 4.2.1)

An available mesocosm study was discussed by the Member State experts. A revised assessment of this study was required. The applicant should provide raw data and the representativeness of the study especially as regarding species diversity should be considered. In particular the effects on chironomids need to be addressed. Furthermore, it was required that multivariate statistical analysis should be presented and taken into consideration when proposing any uncertainty factor. Additionally it was concluded that the study covers only one application and that it needs to be re-evaluated taking into account the PPR Panel opinion on dimoxystrobin[10].

Carbosulfan was rapidly degraded to carbofuran and 7-phenol in the water/sediment study. The metabolite 7-phenol is less toxic to *Daphnia* by a factor of 2000. The mesocosm study is considered to cover the risk to aquatic invertebrates, algae and macrophytes from all metabolites. However the study needs to be reassessed before any conclusion can be drawn.

Carbosulfan showed significant bioaccumulation with a maximum BCF value of 990 in whole fish. At the end of the 30 day depuration period 40%, 28% and 28% of the accumulated residues were still detected in fillet, viscera and whole fish respectively.

[10] Opinion of Scientific Panel on Plant health, Plant protection products and their Residues on a request from EFSA related to the evaluation of dimoxystrobin. The EFSA Journal (2005) 178, 1-45. http://www.efsa.europa.eu/science/ppr/ppr_opinions/833/opinion1.pdf

Data on acute toxicity of the metabolites carbofuran-7 phenol and dibutylamine for species representing fish, aquatic invertebrates and algae show that these metabolites are more than one order of magnitude less toxic than carbosulfan and carbofuran.

5.3. RISK TO BEES

Exposure of bees from the use in citrus and cotton is possible by overspraying of bees foraging on flowering crop or weeds, by ingestion of contaminated nectar, pollen or honey dew and by contact with residues on plants. Carbosulfan and its metabolite carbofuran are systemic compounds and could potentially be found in the pollen following application of the granular formulation. The oral and contact toxicity to bees was tested with carbosulfan. Results from an acute contact toxicity test with carbofuran are also available. However, data on acute oral toxicity of carbofuran is missing. Oral and contact HQ values for carbosulfan are above the Annex VI trigger of 50 indicating a high risk. For the representative uses in citrus and cotton the risk needs to be further addressed by semi-field or field tests. Since sugar beet crop is not flowering and therefore not attractive to bees, the risk from the use of the granular formulation in sugar beet is considered low. For the use of the granular formulation in maize the rapporteur Member State conducted an assessment based on the potential exposure to carbosulfan and carbofuran in pollen. The concentration of both substances in pollen was assumed to be 0.05 mg/kg based on concentrations <0.05 mg/kg in various plant matrices and the toxicity to larvae was assumed to be similar to adults. However, since data on the oral toxicity of carbofuran is missing the assessment was not finalised. A new acute oral toxicity study with carbofuran was submitted by the applicant in July 2005 together with a revised risk assessment. The study and the risk assessment have however not been evaluated by the rapporteur Member State.

5.4. RISK TO OTHER ARTHROPOD SPECIES

The results obtained in laboratory studies with carbusulfan and the formulation MARCHAL 25 EC confirm that carbosulfan is toxic to non-target arthropods (*Typhlodromus pyri*, *Aphidius rhopalosiphi*, *Poecilus cupreus, Pardosa sp.*). A field study with carabid and staphylinid beetles using MARCHAL 10 G was not considered as valid by the rapporteur Member State. It was agreed in the experts' meeting that the risk of the granular formulation to soil dwelling arthropods and foliage dwelling arthropods should be addressed by further semi-field or field studies. An additional laboratory study with *Poecilus cupreus* is available but has not been evaluated. Further studies (LR_{50} and aged residue) using *Aleochara bilineata* and laboratory studies with *Folsomia candida* and *Hypoaspis aculeifer* were provided by the applicant in August 2005. Endpoints derived in the studies with *F. candida* and *H. aculeifer* are reported in the addendum of May 2006, but the studies have not been evaluated by the rapporteur Member State or peer reviewed. However, the assessment provided in the addendum indicates that the risk to *F. candida* is high. Since the use in citrus and cotton is not supported any longer by the applicant no further studies with the formulation MARCHAL 25 CS have been proposed.

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5.5. Risk to earthworms

The risk to earthworms was assessed based on results from a field study performed with the formulation MARCHAL 25 CS at an application rate of 1.3 kg a.s./ha which is above the proposed application rate in maize and sugar beet. Reduction of earthworm populations (number of adult worms, biomass) were observed 1 month after application of carbosulfan. Recovery was observed 6 and 12 months after application. No studies are available with the granular formulation MARCHAL 10 G. It was questioned in the experts' meeting whether the study with MARCHAL 25 CS could be used to assess the risk from the granular formulation and this needs to be clarified before a final conclusion on the risk to earthworms can be drawn for the use in maize and sugar beet.

No studies with soil organisms are available for the metabolite 3-keto carbofuran. The risk needs to be addressed since the active moiety is retained and the metabolite is persistent in acidic soils. Neither are studies with soil organisms available with the metabolite dibutylamine. For this metabolite studies are however not considered necessary since the metabolite does not contain the active moiety.

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

Since the DT_{90} in soil for both carbosulfan and carbofuran is <100 days, additional studies on soil macro-organisms are not required according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).

5.7. Risk to soil non-target micro-organisms

The studies with carbosulfan available in the original DAR were not considered acceptable. A study with MARCHAL 10 G was submitted in July 2005. The results were reported in the addendum of May 2006 but have not been peer reviewed. The rapporteur Member State considered the risk to be low. The impact from the metabolite carbofuran on soil nitrogen turnover and soil respiration rate after 28 days is <25% compared to the control. The risk assessment for soil non-target micro-organisms can only be finalised after a full evaluation of the new study.

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

No information was available to address the risk to non-target plants in the original DAR. A seedling emergence limit test with MARCHAL 10 G was submitted 3 August 2005. In the addendum of May 2006 the rapporteur Member State states that the risk is considered as low. However, no summary of the studies or end points were reported. The risk assessment for non-target organisms can only be concluded when the studies have been fully evaluated.

5.9. Risk to biological methods of sewage treatment

Data from a test with carbosulfan on effects on activated sludge respiration rate are available and indicate that the risk to biological methods of sewage treatment is low.

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6. Residue definitions

Soil

Definitions for risk assessment: carbosulfan, carbofuran, 3-keto-carbofuran and dibutylamine.

Definitions for monitoring: carbosulfan, carbofuran, 3-keto-carbofuran (included pending the finalization of the risk assessment)

Water

Ground water

Definitions for exposure assessment: carbosulfan, carbofuran, 3-keto-carbofuran and dibutylamine.

Definitions for monitoring: carbosulfan, carbofuran, 3-keto-carbofuran and dibutylamine (all compounds included pending the finalization of the assessment)

Surface water

Definitions for risk assessment: carbosulfan, carbofuran and carbofuran-7-phenol, dibutylamine.

Definitions for monitoring: carbosulfan, carbofuran

Air

Definitions for risk assessment: carbosulfan and carbofuran.

Definitions for monitoring: carbosulfan and carbofuran.

Food of plant origin

Definitions for risk assessment: carbosulfan, carbofuran, 3-OH-carbofuran. However approach to assess consumer risk needs to be discussed.

Upon receipt of toxicological data for dibutylamine (DBA) reassessment needed on whether or not DBA to be included.

Definitions for monitoring:

1) carbosulfan to be monitored separately from

2) carbofuran (sum of carbofuran and 3-OH-carbofuran expressed as carbofuran equivalents).

Upon receipt of toxicological data for dibutylamine (DBA) reassessment needed on whether or not DBA to be included

Food of animal origin

Definitions for risk assessment: EPCO 34 provisional proposal 3-OH-carbofuran, however no peer reviewed and agreed proposal available

Definitions for monitoring: EPCO 34 provisional proposal 3-OH-carbofuran, however no peer reviewed and agreed proposal available

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

Soil

Compound (name and/or code)	**Persistence**	**Ecotoxicology**
Carbosulfan	Low to moderate persistent (kinetic data needs to be re-evaluated)	See 5.5 – 5.7
Carbofuran	Low to high persistent (DT_{50lab} = 4.4 – 444 d; $DT_{50field}$ = 1.3 – 125 d)	See 5.5 – 5.7
3-keto-carbofuran	No conclusive data provided, available data in carbofuran dossier indicate that may be high persistent in acidic soils.	No studies with soil organisms are available. The risk needs to be addressed since the active moiety is retained and the metabolite is persistent in acidic soils.
Dibutylamine	No data provided, data required	No studies with soil organisms are available. Studies are not considered necessary since the metabolite does not contain the active moiety.

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 relevance**
Carbosulfan	No acceptable data available	Data required	Yes	Relevant	Relevant

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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 relevance
Carbofuran (Values according data available in carbofuran dossier from a different notifier)	No acceptable data available from carbosulfan notifier. Very high mobile (K_{oc} = 17 – 28 mL / g)	Data required	Yes	Relevant Very toxic (oral LD_{50} 7 mg/kg bw/day and inhalation LC_{50} 0.05 mg/L)	Relevant
3-keto-carbofuran	No data available	Data required	No data available	Relevant Toxic (oral LD_{50} 107 mg/kg bw/day)	No studies available. The metabolite contains the active moiety and needs to be assessed pending the outcome of the $FOCUS_{gw}$ modelling
Dibutylamine	No data available	Data required	No data available	Harmful; Ames test positive	More than one order of magnitude less toxic than carbosulfan and corbofuran. However, pending the outcome of the $FOCUS_{gw}$ modelling an assessment might be needed.

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Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Carbosulfan (water and sediment)	Very toxic to aquatic organisms. For a risk assessment see 5.2
Carbofuran (water and sediment)	Very toxic to aquatic organisms. For a risk assessment see 5.2
Ccarbofuran-7-phenol (only water phase)	More than 3 orders of magnitude less toxic than carbosulfan.
Ddibutylamine (partition properties in water sediment not known)	More than 3 orders of magnitude less toxic than carbosulfan.

Air

Compound (name and/or code)	Toxicology
Carbosulfan	Toxic via inhalation (LC_{50} 0.61 mg/L)
Carbofuran	Very toxic by inhalation (LC_{50} 0.05 mg/L)

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

- Spectra (NMR, MS, IR) of the relevant impurity 5-chlorocarbofuran and *N*-nitrosodibutylamine (date of submission unknown, data requirement identified in the DAR and verified by the meeting of experts (5-chlorocarbofuran) and the EFSA (*N*-nitrosodibutylamine), refer to chapter 1).
- Depending on the assessment of the relevance, spectra (NMR, MS, IR, UV) of the impurity under consideration could be required. (date of submission unknown, data requirement identified in the DAR and verified by the meeting of experts, refer to chapter 1).
- A shelf-life study to demonstrate that the content of the relevant impurities 5-chlorocarbofuran and *N*-nitrosodibutylamine is not increasing upon storage (date of submission unknown, data requirement identified by the EFSA, refer to chapter 1).
- Applicant to provide additional validation data of impurity methods (full validation for impurities 6 and 5-chlorocarbofuran; accuracy for the other impurities) (RMS has received study but not evaluated yet, refer to chapter 1).
- Additional ILV data for the method to determine 3-OH-carbofuran in food of plant origin at levels between 0.05 mg/kg and 0.5 mg/kg (relevant for FMC, date of submission unknown; data gap identified by the meeting of experts, September 2005; refer to chapter 1).
- A new data requirement for information on the genotoxicity of dibutylamine was set, a full *in vitro* data package was required (refer to 2.8).
- Notifier was required to submit data on the levels of nitrosamines in the batches of carbosulfan used in genotoxicity and in carcinogenicity studies (refer to 2.8).
- The results of residue trials in sugar beet and maize have to be presented in a way that a decision on the validity of the trials is possible. Based on this information a conclusion on the availability of sufficient number of valid trials or whether additional trials have to be submitted needs to be taken (data requirement identified by the meeting of experts, date of submission unknown, refer to 3.1.1). Residue trials data have to be supported by storage stability data for all components included in the residue definition.
- Data on rotational crops are required (relevant for the representative uses on maize, sugar beet, cotton; date of submission unknown, refer to 3.1.2).
- Pending the outcome of the required study on the genotoxicity of dibutylamine further residue data (e.g. metabolism studies with soil application investigating the amount of dibutylamin residues in edible crops, residue trials) may be necessary (relevant for all representative uses date of submission unknown, data requirement identified by the EFSA, refer to 3.1.1.).
- Goodness of fitting for all DT_{50} and the end points of the Baumann study (DT_{50}, r^2) need to be reassessed by the applicant (relevant for all uses evaluated; submitted by the applicant in June 2005; neither evaluated nor peer reviewed; refer to chapter 4.1.2).
- Half life of dibutylamine in soil under aerobic conditions has to be determined (relevant for all uses evaluated; position paper provided in June 2005; neither evaluated nor peer reviewed; refer to chapter 4.1.2).

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- PEC soil need to be calculated for metabolite dibutylamine (relevant for all uses evaluated; position paper provided in June 2005; neither evaluated nor peer reviewed; refer to chapter 4.1.2).
- Soil adsorption / desorption properties should be determined for carbosulfan and dibutylamine. A valid study is available for carbofuran from a different notifier in the carbofuran dossier (relevant for all uses evaluated; position paper provided for dibutylamine in June 2005, date of submission unknown for carbosulfan; data gap identified by the meeting of experts; refer to chapter 4.1.3). EFSA note: carbosulfan applicant may wish to submit also K_{oc} for carbofuran since available data pertains to a different applicant.
- Levels of dibutylamine need to be determined in the lysimeter study (relevant for all uses evaluated; position paper provided in June 2005; neither evaluated nor peer reviewed; refer to chapter 4.1.3).
- Available carbofuran lysimeter studies should be submitted (relevant for all uses evaluated; submitted by the applicant in June 2005; neither evaluated nor peer reviewed; refer to chapter 4.1.3).
- $PEC_{SW/SED}$ need to be provided including $PEC_{SW/SED}$ for metabolite dibutylamine (relevant for all uses evaluated; FOCUS SW calculations provided in June 2005, position paper provided for dibutylamine; neither evaluated nor peer reviewed; refer to chapter 4.2.1).
- PEC_{GW} with adequate input parameters should be provided for carbosulfan and metabolites carbofuran, 3-keto-carbofuran and dibutylamine (relevant for all uses evaluated; FOCUS GW calculations for carbofuran and position paper for dibutylamine submitted by the applicant in June 2005; neither evaluated nor peer reviewed; data of submission of PEC GW of soil metabolite 3-keto-carbofuran not known, data gap identified by the meeting of experts; refer to point 4.2.2).
- The risk to birds from ingestion of granules, treated seedlings and contaminated earthworms needs to be addressed. The risk posed by the metabolite carbofuran must be taken into account (relevant for the use in maize and sugar beet; new information provided by the applicant in June/July 2005 and briefly summarised in an addendum of May 2006 but not peer reviewed; refer to point 5.1)
- The long-term risk to mammals from ingested granules and the risk from ingestion of treated seedlings and contaminated earthworms need to be addressed. The risk posed by the metabolite carbofuran must be taken into account (relevant for the use in maize and sugar beet; new information provided by the applicant in June/July 2005 but not evaluated by the RMS; refer to point 5.1)
- A new risk assessment for the aquatic environment based on FOCUS calculations of PEC_{sw} for drainage should be provided (relevant for the use in maize and sugar beet; new information provided by the applicant 18 June 2005 but not evaluated by the RMS; refer to point 5.2)
- Raw data from the existing mesocosm study should be submitted by the applicant (relevant for the use in maize and sugar beet; new information available on 15 March 2006 but not evaluated by the RMS; refer to point 5.2)

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- A revised assessment of the existing mesocosm study especially considering species diversity and effects on chironomids should be provided (relevant for the use in maize and sugar beet; raw data from the mesocosm available on 15 March 2006 but not evaluated by the RMS; refer to point 5.2)
- The pesticidal activity of the metabolites 3-keto-carbofuran and dibutylamine needs to be addressed should these metabolites appear at concentrations >0.1 µg/L in the $FOCUS_{gw}$ modelling (relevant for all evaluated uses; submission date unknown; refer to point 4.2.2)
- An acute oral toxicity study to bees for carbofuran (relevant for the use in maize; study submitted 18 June 2005 but not peer reviewed; refer to point 5.3)
- A revised risk assessment for bees in maize taking into consideration the oral toxicity of carbofuran (relevant for the use in maize; submitted 18 June 2005 but not evaluated; refer to point 5.3)
- Semi-field or field studies with foliage and soil dwelling non-target arthropods (relevant for all evaluated uses; laboratory study with *Poecilius cupreus* submitted 18 June 2005, LR_{50} and aged residue studies with *Aleochara bilineata* submitted 3 August 2005, laboratory studies with *Folsomia candida* and *Hypoaspis aculeifer* submitted 3 August 2005; toxicity end points for *F. candida* and *H. aculeifer* were reported in the addendum of May 2006 but not peer reviewed, refer to point 5.4)
- Further justification is needed to clarify whether the earthworm field study performed with the formulation MARCHAL 25 CS can be used for the risk assessment for MARCHAL 10 G (relevant for the use in maize and sugar beet; submission date unknown; refer to point 5.5)
- The risk to soil organisms from exposure to the metabolite 3-keto-carbofuran needs to be addressed since the active moiety is retained and the metabolite is persistent in acidic soils (relevant for all evaluated uses; data gap identified by EFSA, submission date unknown; refer to point 5.5)
- A study on effects to soil non-target micro-organisms (relevant for all evaluated uses; a study with MARSHAL 10 G was submitted in July 2005 and the results were reported in the addendum of May 2006 but have not been peer reviewed, refer to point 5.7)
- The risk to non-target flora should be addressed (relevant for all evaluated uses; a study on seedling emergence using MARSHAL 10 G was submitted 3 August 2005 but has not been evaluated by the RMS; refer to point 5.8)

Requirements, as far as identified, for the CS formulation withdrawn by the applicant for the EU peer review process (i.e. with respect to Annex I inclusion).

- Additional residue trials are required to address residue situation in cotton and citrus (oranges, mandarins) sufficiently (date of submission unknown, data requirement identified in the DAR and verified by the meeting of experts, refer to 3.1.1). Residue trials data have to be supported by storage stability data for all components included in the residue definition.
- A study simulating relevant household/industrial processing conditions has to be provided (relevant for the use on citrus crops; provided position paper was evaluated in addendum Feb 2006, but not peer reviewed; refer to 3.1)

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- The risk to insectivorous birds needs to be addressed (relevant for the use in citrus and cotton; use no longer supported by the applicant; refer to point 5.1)
- The risk to herbivorous birds needs to be addressed (relevant for the use in cotton; use no longer supported by the applicant; refer to point 5.1)
- The risk to small herbivorous mammals needs to be addressed (relevant for the use in citrus; use no longer supported by the applicant; refer to point 5.1)
- A new mesocosm study with 2 applications (relevant for the use in cotton and citrus¸ use no longer supported by the applicant; refer to point 5.2)
- The risk to bees foraging in cotton needs to be addressed (application during flowering, LD_{50} for Marchal 25 CS is missing, further semi-field or field studies are required) (relevant for the use in cotton; use no longer supported by the applicant; refer to point 5.3)
- The risk to bees foraging in citrus needs to be addressed (presence of flowering weeds, possible off-crop effects, presence of honey dew, LD_{50} for Marchal 25 CS is missing, further semi-field or field studies are required) (relevant for the use in cotton; use no longer supported by the applicant; refer to point 5.3)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as insecticide as proposed by the applicant which comprises incorporation into soil (at drilling) to control soil insects, where maize and sugar beet will be grew. The application rate is 0.75 kg carbosulfan per hectare. Carbosulfan can be used as insecticide and nematicide. It should be noted that during the peer review process only the use as insecticide was evaluated.
The representative formulated product for the evaluation was "Marshal 10G", a granule (GR), registered in some Member States of the EU.
It should be noted that the applicant no longer supports the second formulation, presented in the dossier and DAR ("Marshal 25CS"). Consequently the uses on citrus and cotton are no longer supported.

Adequate methods are available to monitor all compounds given in the respective residue definition for food of plant origin, soil and water.
Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that at least limited quality control measurements of the plant protection product are possible.

Carbosulfan is toxic if swallowed and should be classified as **T, R25 "Toxic if swallowed".** It is of low toxicity via dermal route and toxic via inhalation (classification as **T, R23** is proposed).

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Carbosulfan is not a skin or eye irritant but is a skin sensitiser and should be classified **R43 "May cause sensitisation by skin contact".** Carbosulfan gave negative results in *in vitro* and *in vivo* genotoxicity tests and did not show any carcinogenic potential. Nevertheless, the level of impurities in batches used for toxicological studies remains a concern. In the three-generation rat study, the relevant maternal and reproductive NOAEL was 1.2 mg/kg bw/day. In developmental toxicity studies in rats and rabbits, the relevant maternal and developmental NOAEL was 2 mg/kg bw/d. Carbosulfan displayed no potential for induced delayed neurotoxicity. The provisional reference values are as follows: ADI and ARfD are 0.01 mg/kg bw/day; AOEL is 0.02 mg/kg bw/day. The risk assessment for operators has to be considered as inconclusive until the AOEL is confirmed. However, it can be assumed that bystander and worker exposure is likely to be negligible under the supported conditions of use.

The metabolism, distribution and residue behaviour of carbosulfan was investigated in various crops with different methods of application. In studies on sugar beet, soybean, maize and rice plants, uptake, distribution and metabolism of residues was investigated following an application of carbosulfan to the soil. Additionally, carbosulfan metabolism after foliar application to oranges, alfalfa and sugar beet was studied. In all cases, metabolism of carbosulfan was initiated by the cleavage of the S-N bond into carbofuran and dibutylamine, proceeding with hydroxylation or hydrolysis and oxidation steps to yield 3-OH-carbofuran and phenolic derivates of carbofuran, which were further conjugated. It can be concluded that the metabolic pattern observed in plants treated with carbosulfan was independent from the mode of application whereas quantitative differences were noted, mainly with regard to the percentage of carbosulfan found in the crops.
At the time being, carbosulfan, carbofuran and 3-OH-carbofuran were considered the relevant residues to assess consumer exposure and consumer risk. However, the metabolite dibutylamine is still under discussion concerning its possible genotoxicity and ought to be therefore considered a potential candidate to include in the residue definition, too.
Moreover a need to address residues of dibutylamine but also carbofuran and its metabolites in succeeding crops following application of carbosulfan was identified.
Based on the currently proposed residue definition, supervised residue trials in sugar beet and maize indicated that residues were low and mostly below the respective LOQ. However, the available residue trials have to be reconsidered for their validity and sufficiency. With regard to the metabolite dibuytlamine no residue data have been reported. Further residue data in cotton seed and citrus will be needed if foliar uses are reinstated in the future. Since the assessment of plant residues still needs to be finalized and due to the lack of peer reviewed evaluation of relevant data and information it is not possible to conclude on whether or not significant residues may occur in edible animal matrices.
The consumer risk assessment should be considered as inconclusive due to the uncertainties caused by lacking data identified during the evaluation.

Degradation of carbosulfan in soil under laboratory aerobic conditions produces carbofuran (max. 48.7 % - 69.3 % AR after 7 d) as the main metabolite. Also 3-keto-carbofuran is produced in significant amounts (max. 5.3 % - 6.6 %). The meeting of MS experts considered that this metabolite

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needs to be further assessed as it contains the active carbamate moiety. The mineralization was very limited (max CO_2 2.3 % AR) and bounded residues increased up to maximum of 90 % AR after 100 d. In a soil degradation study performed with ^{14}C-dibutylamine labelled carbosulfan, dibutylamine (max 21.5 % AR after 3 d) was found as a major aerobic soil metabolite.

No valid degradation study of carbosulfan in soil under anaerobic conditions is available. Also photolysis in soil was not investigated. Two soil photolysis studies are available for the main metabolite carbofuran in the corresponding DAR. On basis of these studies, carbofuran was considered stable to photolysis in soil.

Evaluation meeting agreed that a re-evaluation of the degradation kinetic in degradation studies, including assessment of the goodness of fit, had to be performed by the applicant. Reassessment is available but has not been evaluated and peer reviewed. Therefore, it has not been possible to agree on laboratory degradation end points for carbosulfan.

Summaries of some field dissipation studies performed with carbosulfan in EU are available. Half life of carbosulfan in these trials ranges between 0.35 to 31.3 d. Half life of metabolite carbofuran in the these trials ranges between 1.3 to 71.9 d. EFSA notes that in the context of the carbofuran discussion, the meeting of MS experts was not able to determine the reliability of these studies. A position paper from the applicants is available (June 2005) but has still not been assessed and peer reviewed.

PEC in soil were calculated in the DAR for carbosulfan and carbofuran based on the field worst case half lives (DT_{50} carbosulfan = 35 d, DT_{50} carbofuran = 71.9 d) and the representative uses in maize, sugar beet, citrus and cotton.

No degradation parameters are available for soil metabolite dibutylamine. Evaluation meeting agreed that half life of dibutylamine in soil and PEC soil for this metabolite need to be determined. A position paper is already available but has still not been evaluated and peer reviewed.

In the batch adsorption / desorption study available carbosulfan showed to be slight to low mobile in soil, carbofuran very high mobile and dibutylamine medium to high mobile in soil. The rapporteur Member State concluded in the DAR that this study is of limited quality. The meeting of MS experts agreed that the study was not valid due to serious methodological flaws and therefore identified a data gap for a valid adsorption study for carbosulfan and dibutylamine. For the metabolite carbofuran an additional study (from a different notifier Dianica; Mamouni, 2002) is available in the dossier of carbofuran as active substance.

A lysimeter study performed with two lysimeters in loamy sand soil is available. However, annual average concentrations and detailed characterization of the residue are missing in this study. Evaluation meeting agreed that the levels of soil metabolite dibutylamine need to be determined in the lysimeter leachate samples and that the two new lysimeters performed with carbofuran (carbosulfan metabolite) should be submitted and assessed. These studies and a position paper are already available but have not been evaluated and peer reviewed. Carbosulfan hydrolyses with half lives lower than 1 d at pH 5 and 7 and with a half life of 7 d at pH 9. Main hydrolysis products are carbofuran and dibutylamine. Carbofuran subsequently degrades to carbofuran-7-phenol.

Photolysis may contribute to the environmental degradation of carbosulfan in water. Two regions of polar degradation products (amounting to 66.7 % AR) were found but not characterized in the aqueous photolysis study. The environmental relevance of these metabolites is uncertain and was not

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examined by the meeting of MS experts since the study was still not evaluated at the time the fate and behaviour in the environment meeting took place.

Carbosulfan is not readily biodegradable according the available study.

Carbosulfan was low persistent in aerobic water / sediment systems ($DT_{50\ \text{whole system}\ 20\ ^\circ C}$ = 4.2 – 5.4 d; $DT_{50\ \text{whole system}\ 10\ ^\circ C}$ = 10 d). Main metabolites formed were carbofuran (max. 34.7 % AR in water; max. 20.1 % AR in sediment) and carbofuran-7-phenol (max. 11.6 % AR in water; max. 3.21 % AR in sediment). A non characterized metabolite (Unknown 3) also appears at levels above 10 % AR in the sediment of some systems (max. 20.11 % AR after 7 d). This compound has been tentatively identified as a structure that contains the carbamate moiety and may be expected to produce carbofuran when degraded. The amount of bound residues increased steadily up to 30.5 – 43.0 % AR at the end of the experiments (102 d).

No half lives are reported in carbosulfan DAR for metabolites carbofuran and carbofuran-7-phenol in the water / sediment systems. From water / sediment studies summarized in the carbofuran DAR, carbofuran degraded in the whole system with a first order half life of approximately 41 d. Available water sediment studies under alkaline conditions (from carbofuran applicant Dianica) show the faster degradation of carbofuran and the formation of carbofuran-7-phenol at high levels under these conditions.

$PEC_{SW/SED}$ were calculated by the applicant based on an *ad hoc* modelling exercise. Evaluation Meeting confirmed the rapporteur Member State data requirement for FOCUS SW $PEC_{SW/SED}$ and agreed that PEC_{SW} for dibutylamine need to be calculated. FOCUS SW calculations and a position paper for dibutylamine are already available but have still not been evaluated and peer reviewed.

The applicant presented an estimation of the potential for ground water contamination based on the FOCUS GW scheme (PRZM). The rapporteur Member State considered that half life and K_{oc} employed for carbofuran in the calculation were not justified and proposed a data requirement for new PEC_{GW}. This data requirement was confirmed by the Evaluation Meeting that additionally required calculation of PEC_{GW} for metabolite dibutylamine. New FOCUS GW calculations for carbofuran and a position paper for dibutylamine are available but have still not been evaluated and peer reviewed. Additionally, experts meeting indicated that potential ground water contamination by soil metabolite 3-keto-carbofuran should be addressed. This is a new data gap identified by the meeting of experts.

It is not expected that carbosulfan may contaminate the air compartment or be prone to long range transport through air. Data in carbofuran dossier shows that contamination of the air compartment and long range transport thought air is not expected for carbofuran.

An addendum to the fate and behaviour chapter has been provided the 18th of May 2006. When reported, the information in the addendum has been summarized too briefly to draw any conclusion on its reliability. Studies or reports presumably submitted by the applicant are not adequately referenced. Therefore studies submitted by the applicant after the DAR was submitted are considered neither evaluated nor peer-reviewed in this conclusion.

The first tier risk assessment based on generic species identified a potential risk to insectivorous birds in citrus and cotton, to medium herbivorous birds in cotton and to small herbivorous mammals in

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citrus from foliar application of carbosulfan. Only a small number of granules have to be ingested by a small bird to reach the acute LD_{50} or the LC_{50}, hence the risk of ingestion of granules should be further addressed. The number of granules that have to be ingested by a small mammal to reach the LD_{50} is relatively high and since granules are not attractive to mammals the acute risk is considered to be low. Few granules are however needed to reach the NOAEL for mammals and the long-term risk needs to be further addressed. Also the risk from ingestion of treated seedlings, contaminated earthworms, fish and drinking water needs to be evaluated.

Carbosulfan and the metabolite carbofuran are classified as very toxic to aquatic organisms. For citrus and cotton the risk assessment indicates acute and long-term risk to aquatic organisms even with 50 m buffer zones based on contamination by spray drift only. Based on available data for PEC_{sw}, a long-term risk is indicated for all representative uses evaluated from exposure to the metabolite carbofuran. The assessment needs to be refined based on FOCUS modelling of PEC_{sw}.

Carbosulfan is toxic to bees. For the representative uses in citrus and cotton the risk needs to be further addressed by semi-field or field tests. Since sugar beet crop is not flowering the risk from the use in sugar beet is considered low. The risk to bees from exposure to carbosulfan/carbofuran in nectar and pollen following granular application was not assessed due to non evaluated data on oral toxicity for carbofuran. Laboratory studies confirm that carbosulfan is toxic to arthropods. Further semi-field or field studies are required to evaluate the risk. The risk to earthworms from the use of MARCHAL 25 CS is considered as low. For the granular formulation further clarification is needed on whether the field study with MARCHAL 25 CS can be used for the assessment. No evaluation of the risk to soil micro-organisms and non-target plants is available. For biological methods of sewage treatment the risk is considered to be low.

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

- Personal as well as respiratory protective equipment is needed for operators (treated area 15 ha/day) see 2.12).
- Based on current data for PEC_{sw} risk mitigation measures comparable to buffer zones >50 m are needed for the use in cotton and citrus to protect the aquatic environment.

Critical areas of concern

- At the moment no final specification in terms of maximum level for the impurities in the technical material can be set, due to some missing validation data for the respective analytical methods.
- At the moment no validated analytical method is available for the determination of the relevant impurity 5-chlorocarbofuran (refer to chapter 1 and to the "List of studies to be generated or still ongoing").
- Carbosulfan is toxic if swallowed and via inhalation.

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- The impurity N-nitrosdibutylamine is classified as Category 2B carcinogen by IARC and is exceeding the level of 1 mg/kg. The level of N-nitrosdibutylamine in the batches used in mutagenicity and carcinogenicity studies is not known. Thus, the possible toxicological impact the impurity might have has not been adequately addressed in the toxicological data package. A data gap was identified for the RMS
- The reference values agreed during the EPCO meeting should be regarded as provisional, due to the number of data gap identified during the process. The role of nitrosamines in determining health effects should be assessed with regard to their level in toxicological batches and their intrinsic properties have to be regarded as of concern, possibly leading to an increase of the safety factors applied. Also the missing acute and subchronic neurotoxicity studies might have an impact on some of the reference values.
- The risk assessment for operators is considered to be inconclusive until the AOEL is confirmed.
- The consumer risk assessment and proposed MRLs related to the representative uses of carbosulfan is not conclusive due to the number of data gaps identified during the process. The reference values for carbosulfan and for carbofuran are provisional. An evaluation of whether the metabolite dibutylamine might be of concern in terms of consumer safety is not possible due to lacking data. Moreover it is not possible to conclude on the potential occurrence of relevant residues in food of animal origin and in rotational crops.
- Numerous data requirements were identified in the DAR and in the Evaluation Meeting. The applicant has submitted new studies and information to address some of these. The new data were not evaluated by the RMS and thus not peer reviewed. Further data gaps were identified in the meeting of experts. No conclusion on potential ground water contamination by carbosulfan and its metabolites can be reached.
- Numerous data requirements were identified in the DAR and in the experts' meeting for the section ecotoxicology. The risk was assessed as low for bees in sugar beet, earthworms in citrus/cotton and for biological methods of sewage treatment. For all other groups of organisms a high risk could not be excluded based on available peer reviewed data. In particular for birds, mammals, aquatic organisms and bees (except in sugar beet) a first tier high risk was identified. The applicant has submitted new studies and information to address some of the data gaps. The new data were however not evaluated by the RMS and thus not peer reviewed. A final conclusion on the risk to non-target organisms can only be drawn once all data requirements have been fulfilled and the data evaluated.

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APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Carbosulfan
Function (e.g. fungicide)	Insecticide, nematicide

Rapporteur Member State	Belgium
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	2,3-dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio)methylcarbamate
Chemical name (CA) ‡	2,3-dihydro-2,2-dimethyl-7-benzofuranyl [(dibutylamino)thio]methylcarbamate
CIPAC No ‡	417
CAS No ‡	[55285-14-8]
EEC No (EINECS or ELINCS) ‡	EINECS 259-565-9
FAO Specification ‡ (including year of publication)	417/TC/S/F (1991), published in AGP: CP/315 (1995) : Purity "The Carbosulfan content shall be declared (not less than 890 g/kg) and, when determined, the content obtained shall not differ from that declared by more than ± 25 g/kg" Impurities Carbofuran - max. 20 g/kg Water - max. 2 g/kg
Minimum purity of the active substance as manufactured ‡ (g/kg)	Technical Carbosulfan (as manufactured, before addition of stabilizer): min. 890 g/kg Stabilized technical Carbosulfan (MUP = manufacturing use product) : min. 865 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	Carbofuran - max. 20 g/kg 5-chlorocarbofuran - max. 2 g/kg ***N-nitrosodibutylamine content to be addressed.*** ***The relevance of a fourth impurity is under discussion.***

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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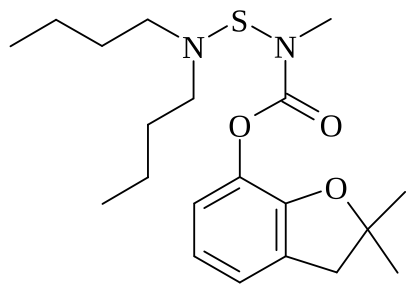
Molecular formula ‡	$C_{20}H_{32}N_2O_3S$
Molecular mass ‡	380.5
Structural formula ‡	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	No clearly defined freezing point (98.5%)
Boiling point (state purity) ‡	219.3 °C (98.5%)
Temperature of decomposition	219.5 °C (98.5%) decomposition of carbosulfan occurs a few moments after the beginning of boiling
Appearance (state purity) ‡	Medium yellow viscous liquid, no odour to perhaps a barely noticeable amine odour (98.5%)
Relative density (state purity) ‡	D_4^{20} = 1.0445 (98.5%)
Surface tension	Not applicable (instability in water)
Vapour pressure (in Pa, state temperature) ‡	3.59 x 10^{-5} Pa at 25 °C (98.5%)
Henry's law constant (Pa m^3 mol^{-1}) ‡	124.21 x 10^{-3} Pa.m³.mol^{-1} (98.5%)
Solubility in water ‡ (g/L or mg/L, state temperature)	pH 9, 25°C : 0.11 mg/L (98.5%) no effect of pH (no dissociation in water)
Solubility in organic solvents ‡ (in g/L or mg/L, state temperature)	solubility at 23 °C hexane: miscible in all proportions toluene: miscible in all proportions acetone: miscible in all proportions acetonitrile: miscible in all proportions solubility at 20 °C (g/L) dichloromethane: > 250 methanol: > 250 ethyl acetate: > 250
Partition co-efficient (log POW) ‡ (state pH and temperature)	25 °C: 7.42 (98.5%) no effect of pH (no dissociation in water)
Hydrolytic stability (DT_{50}) ‡ (state pH and temperature)	pH 5, 25 °C : DT_{50} = 0.2 hr

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	pH 7, 25 °C : DT_{50} = 11.4 hr
	pH 9, 25°C : DT_{50} = 173.3 hr (ca 7 d)
Dissociation constant ‡	No dissociation in water
UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	In acetonitrile: λ_{max} 200 nm; ε = 4.342 x 10^4 $L.mol^{-1}.cm^{-1}$ λ_{max} 277.5 nm; ε = 3.144 x 10^3 $L.mol^{-1}.cm^{-1}$ in acetonitrile/water 50/50 at λ 292 nm : ε = 274 $L.mol^{-1}.cm^{-1}$
Photostability (DT_{50}) ‡ (aqueous, sunlight, state pH)	Suntest CPS (filtered xenon lamp) : pH 9, 22 °C : DT_{50} = 14 hrs
Quantum yield of direct phototransformation in water at λ > 290 nm ‡	ϕ: 1.21 x 10^{-6}
Flammability ‡	Flash point : 136.7 °C (89.3%, nonstabilized) flash point : 158.9 °C (85.9%, stabilized) auto-ignition temperature : 360 °C (88.4%)
Explosive properties ‡	Not explosive

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List of representative uses evaluated*

Crop and/or situation (a)	Member State or 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 a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applica tions (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Maize	EU	Marshal 10G	F	*Elateridae spp,. Scutigerella spp., Atomaria linearis, Aphis spp., Blaniulus spp. Oscinella frit, Phyllocnistis spp***.**	GR	100 g/kg	Mechanical incorporation into soil	At drilling	1	na	na	na	0.75	PHI : not applicable as applied at drilling	Granule dropped into seed furrow. Soil then folder over to cover. [1] [2]
Sugar Beet	EU	Marshal 10G	F	*Elateridae spp, Scutigerella spp., Atomaria linearis, Aphis spp., Blaniulus spp. Oscinella frit, Phyllocnistis spp*	GR	100 g/kg	mechanical incorpor-ation into soil	At drilling	1	na	na	na	0.75	PHI : not applicable as applied at drilling	Granule dropped into seed furrow. Soil then folded over to cover. [1] [2]
Citrus	EU	Marshal 25CS	F	*Planococcus citri, Saissetia oleae, aphids*	CS	250 g/L	Orchard spray	July/ August (approx BBCH 75)	2	14 days	0.0375 to 0.05	1500 to 2000	0.750	60	[1] [2] [3]

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Cotton	EU	Marshal 25CS	F	*Aphid, thrips*	CS	250 g/L	Foliar spray	July/ August (approx. BBCH 60 to BBCH 72)	2	14 days	0.075	400 to 500	0.375	30	[1] [2] [3]

[1] A risk and several data requirements were identified in section 4 and 5.
[2] The risk assessment has to be considered as inconclusive until the AOEL is confirmed, data gaps are also identified, section 2 (Mammalian Toxicology)
[3] The risk assessment for the CS formulation was not completed since the applicant does not support this formulation for the review at EU level.

Remarks:	*	Uses for which risk assessment could not been concluded due to lack of essential data are marked grey	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
	(a)	For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)	(i)	g/kg or g/L
	(b)	Outdoor or field use (F), glasshouse application (G) or indoor application (I)	(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
	(c)	*e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds		
	(d)	*e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)	(k)	Indicate the minimum and maximum number of application possible under practical conditions of use
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		
	(f)	All abbreviations used must be explained	(l)	PHI - minimum pre-harvest interval
	(g)	Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench	(m)	Remarks may include: Extent of use/economic importance/restrictions

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Appendix 1.2: Methods of Analysis

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

Technical as (principle of method)	HPLC-UV; CIPAC Method 417/TC/M/3 : HPLC-UV (ISTD)
Impurities in technical as (principle of method)	Carbofuran and 5-chlorocarbofuran: HPLC-UV GC-MSD IC with conductivity detector GPC-UV GPC with Refractive Index detector ***Validation data required (incl. 5-chlorocarbofuran)*** ***Additional validation was submitted for impurity methods; remains to be evaluated by RMS***
Plant protection product (principle of method)	*Carbosulfan:* CIPAC Method 417/GR/M/3 (HPLC-UV (ISTD)) *Carbofuran:* HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	GC-MSD (carbosulfan, carbofuran, 3-hydroxy carbofuran); LOQ = 0.05 mg/kg (for each analyte; dry crops, commodities with high fat content) GC-NPD (carbosulfan, carbofuran, 3-hydroxy carbofuran); LOQ = 0.05 mg/kg (for each analyte;commodities with high water content, fruits with high acid content) HPLC-PCD with Flu (carbosulfan, carbofuran, 3-hydroxy carbofuran); LOQ = 0.05 mg/kg (for each analyte;commodities with high water content) ***Additional ILV data for 3-hydroxy-carbofuran required***
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not required (no MRLs proposed)
Soil (principle of method and LOQ)	HPLC-PCD with Flu (carbosulfan, carbofuran) and GC-MS (dibutylamine); LOQ = 0.005 mg/kg (for each analyte)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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Water (principle of method and LOQ)	HPLC-PCD with Flu (carbosulfan, carbofuran, 3-hydroxy carbofuran); LOQ = 0.1 µg/L (for each analyte; drinking water, surface water) ***Depending on the final residue definition for groundwater, additional methodology may be required***
Air (principle of method and LOQ)	*Not required (the application techniques (i.e. granular formulation to be incorporated in soil) is such that no relevant exposure is likely to occur)* HPLC-PCD with Flu (Carbosulfan); LOQ = 6 ng/m³ (warm, humid air)
Body fluids and tissues (principle of method and LOQ)	HPLC-PCD with Flu (carbosulfan, carbofuran, 3-hydroxy carbofuran, 3-keto carbofuran); LOQ = 0.05 mg/kg (for each analyte; tissues, blood)

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None

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Appendix 1.3: Impact on Human and Animal Health

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

Rate and extent of absorption ‡	High bioavailability (>70%) within 24 h (4 and 30 mg/kg bw rat)
Distribution ‡	Large, highest level in excretory organs and carcass
Potential for accumulation ‡	No evidence of accumulation
Rate and extent of excretion ‡	Rapid and extensive (app.90%) within 24 h mainly via urine (63-77%)
Metabolism in animals ‡	Extensive metabolism (> 80%): hydrolysis at C-7 to form 7-phenol and at N-S to form carbofuran and dibutylamine. 7-phenol and carbofuran are oxidized at C-3 generating 3-OH-metabolites. Dibutylamine is oxidized to CO_2 and volatiles.
Toxicologically significant compounds ‡ (animals, plants and environment)	Carbosulfan and metabolites containing the carbamate moiety (animals and plants), dibutylamine

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	138 mg/kg bw (42.7 mg/kg bw, rabbit))	**T; R25**
Rat LD_{50} dermal ‡	3700 mg/kg bw	
Rat LC_{50} inhalation ‡	0.61 mg/L	**T; R23**
Skin irritation ‡	Non- irritant	
Eye irritation ‡	Non- irritant	
Skin sensitization ‡ (test method used and result)	Sensitising (Buehler 10 induction)	**Xi; R43**

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Inhibition of acetyl cholinesterase (rat)
Lowest relevant oral NOAEL / NOEL ‡	2 mg/kg bw/day, 90 day rat
Lowest relevant dermal NOAEL / NOEL ‡	5 mg/kg bw/day, 21 day rabbit
Lowest relevant inhalation NOAEL / NOEL ‡	0.00015 mg/L, 28 day rat

Genotoxicity ‡ (Annex IIA, point 5.4)

…………………………………………	Not genotoxic *in vitro* and *in vivo* However, possible impact of impurity remain a concern

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

Target/critical effect ‡	Acetyl cholinesterase inhibition, focal iris atrophy and degenerative retinopathy (rat)
Lowest relevant NOAEL / NOEL ‡	1 mg/kg bw/day, 104 week
Carcinogenicity ‡	No carcinogenic potential However, possible impact of impurity remain a concern

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	Reduced number born pups, litter size, pup weight at parental toxic doses (rat)
Lowest relevant reproductive NOAEL / NOEL‡	Maternal and reproductive: 1.2 mg/kg bw/day
Developmental target / critical effect ‡	Rat: incomplete ossification at maternal toxic dose
Lowest relevant developmental NOAEL / NOEL ‡	Maternal and developmental: 2 mg/kg bw/day

Neurotoxicity / Delayed neurotoxicity ‡ (Annex IIA, point 5.7)

………………………………………	No delayed neuropathy in hens LD_{50} 376 mg/kg bw

Other toxicological studies ‡ (Annex IIA, point 5.8)

Impurity N-nitrosodibutylamine	IARC considered N-nitrosodibutylamine a category 2B carcinogen.

Metabolites

The information presented on carbofuran and other metabolites was agreed on in the context of the assessment of the active substance carbofuran. Further details are given in the EFSA conclusion on carbofuran.

Carbofuran[11] Acute toxicity	Rat LD_{50} oral: 7 mg/kg bw	**T^+; R28**
	Rat LD_{50} dermal: 1000 - 2000 mg/kg bw	**Xn; R21**
	Rat LC_{50} inhalation: 0.05 mg/L	**T^+; R26**
	Skin irritation: non- irritant	
	Eye irritation: non- irritant, but mortality reported (rabbits)	**T; R39/41**

[11] It should be noted that the applicant for benfuracarb has access to the carbofuran dossier from Dianica.

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	Skin sensitization ‡ (test method used and result) Non- sensitizer (Buehler and M&K)
Short term toxicity (carbofuran)	<u>Target / critical effect:</u> testicular degeneration, clinical signs of neurotoxicity related to AChE inhibition (rat and dogs) <u>Lowest relevant oral NOAEL / NOEL</u> 0.1 mg/kg bw/day, 1-year dog and 60 day, rat (published study) <u>Lowest relevant dermal NOAEL / NOEL</u> 25 mg/kg bw/day, 21 day rabbit <u>Lowest relevant inhalation NOAEL / NOEL</u> No study available
Genotoxicity (carbofuran)	Positive results in bacterial tests; Negative in *in vivo* tests
Long term toxicity and carcinogenicity (carbofuran)	<u>Target/critical effect:</u> Body weight and AChE inhibition <u>Lowest relevant NOAEL / NOEL:</u> 0.462 mg/kg bw/day, 2 year rat <u>Carcinogenicity:</u> No carcinogenic potential
Reproductive toxicity (carbofuran)	<u>Reproduction target / critical effect</u> Reduced litter parameters in rat multigeneration study Testicular and sperm toxicity (published study, rat) **R62?**
	<u>Lowest relevant reproductive NOAEL / NOEL</u> Parental and reproduction: 1.2 mg/kg bw/day <u>Developmental target / critical effect</u> Fetotoxicity and developmental neurotoxicity at maternal toxic doses (rat). <u>Lowest relevant developmental NOAEL / NOEL</u> <u>Rat:</u> Developmental: 1 mg/kg bw/day Maternal: 0.1 mg/kg bw/day <u>Rabbit:</u> Developmental and maternal: 0.5 mg/kg bw/day
Neurotoxicity / delayed neurotoxicity (carbofuran)	<u>Delayed neurotoxicity</u> No delayed neuropathy in hens NOAEL neurotoxicity 0.5 mg/kg bw

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	Subchronic neurotoxicity test 3.2 mg/kg bw/day, 13-week rat
Other toxicological studies (carbofuran)	Mechanistic study AChE inhibition: no difference in sensitivity to AChE inhibition with age.
ADI[12] (carbofuran)	0.001 mg/kg bw/d (1-year dog study, SF: 100)
AOEL[12] (carbofuran)	0.001 mg/kg bw/d (1-year dog study, SF: 100)
ARfD[12] (carbofuran)	0.001 mg/kg bw/d (Developmental rat study, maternal toxicity, SF: 100)
3-OH-carbofuran:	LD_{50} oral: 8.3 mg/kg bw Positive in Ames test strain TA1537 with S9 mix Positive in TK locus in L5178Y mouse lymphoma cells with and w/o S9 mix **T+, R28**
3-OH-7-phenol:	LD_{50} oral: 1654 mg/kg bw **Xn, R22**
Dibutylamine	Oral LD_{50} 205mg/kg bw/day **Xn, R22** Genotoxicity: inconclusive

Medical data ‡ (Annex IIA, point 5.9)

	No subjective/objective adverse symptoms were observed during medical examination of workers engaged in production of carbosulfan

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI [13]‡	*0.01 mg/kg bw/d*	Rat, 2-year	100
AOEL [13]‡	*0.02 mg/kg bw/day*	Rat, 90 day studies	100
ARfD [13]‡ (acute reference dose)	*0.01 mg/kg bw/d*	Rat, 2-year	100

Dermal absorption (Annex IIIA, point 7.3)

Marshal 10G	Default value of 100%

[12] Values and SF are provisional, might be confirmed pending vote of ECB
[13] Reference values are provisional due to missing neurotoxicity studies and data gap on the amount of the impurity N-nitrosdibutylamine in toxicological batches (in particular genotoxicity and long term studies)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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Acceptable exposure scenarios (including method of calculation)

Operator	***The risk assessment for operators is considered as inconclusive until the AOEL is confirmed.***
Workers	Granular formulation: no exposure
Bystanders	Granular formulation: no exposure

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	T;	Toxic
	Xi	Irritating
	R23	Toxic via inhalation
	R25	Toxic if swallowed
	R43	May cause sensitisation by skin contact

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.4: Residues

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

Plant groups covered	Sugar beet (R), maize and - rice (C), soybean (P/O), (soil application) oranges (F) and alfalfa (C).(foliar application)
Rotational crops	Not submitted, however, the metabolism and behaviour of carbosulfan following uptake via the roots can be considered sufficiently investigated in cereals
Plant residue definition for monitoring	-Carbosulfan, -Carbofuran (sum of carbofuran and 3-OH-carbofuran expressed as carbofuran equivalents). Upon receipt of toxicological data for dibutylamine (DBA) reassessment needed on whether or not DBA to be included
Plant residue definition for risk assessment	-Carbosulfan, -Carbofuran (sum of carbofuran and 3-OH-carbofuran expressed as carbofuran equivalents). Upon receipt of toxicological data for dibutylamine (DBA) reassessment needed on whether or not DBA to be included
Conversion factor (monitoring to risk assessment)	None

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

Animals covered	Lactating goats and laying hens.
Animal residue definition for monitoring	Not peer reviewed and agreed proposal available, EPCO 34 provisional proposal 3-OH-carbofuran
Animal residue definition for risk assessment	Not peer reviewed and agreed proposal available, EPCO 34 provisional proposal 3-OH-carbofuran
Conversion factor (monitoring to risk assessment)	Not applicable
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	Yes

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

………………………..……………	Not required for carbosulfan since Carbosulfan is degraded very rapidly into carbofuran. Still to be addressed for carbofuran and DBA

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

………………………………………	- The residues of the carbamates and the phenol metabolites can be considered as stable in all the orange processed matrices under frozen storage conditions for a period of 12 months. - The carbosulfan content decreased significantly (more than 30 %) within 21 months for green alfalfa, 2 weeks for cabbage, 3 months for corn foliage and 6 months for potatoes. - No data available on the stability of carbofuran and 3-OH-carbofuran in other crops - The dibutylamine moiety was stable in all cow matrices (milk, muscle and liver) for at least 6 months. - Residues of carbosulfan and its metabolites couldn't be considered as stable in milk, muscle and liver probably because of the presence of hydrolytic enzymes.

Residues from livestock feeding studies [14] (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes	Poultry: no	Pig: Yes [15]
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-		
Eggs		-	

[14] Cannot be assessed without agreed residue definition for food of animal origin
[15] A feeding study in pigs is not required as metabolic pathways in rat and in cows were considered as similar

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Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	Provisional MRLs (mg/kg)	STMR (mg/kg) (b)
Sugar beet [16]	NE	**root: [17] -*carbosulfan* : 0.248, 0.063, 10 x <0.05 mg/kg -*carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: <0.1, <0.1, <0.1, <0.1, 0.112, <0.1, <0.1, <0.1, <0.1, <0.1, <0.1, <0.1 mg/kg **Leaves: -*carbosulfan* : 12x <0.05 mg/kg -carbofuran + 3-OH-carbofuran expressed as carbofuran equiv.: 12x <0.1 mg/kg.	Samples of leaves/tops and roots at different PHIs up to normal harvest time were analysed for carbosulfan and its metabolites carbofuran and 3-OH-carbofuran. Decay curves are given with last sampling 129 to 173 days after the application. Trials performed in accordance with the critical GAP	*Carbosulfan*: 0.05* mg/kg *Carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: 0.1* mg/kg	*Carbosulfan*: 0.05* mg/kg *Carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: 0.1* mg/kg
	SE	**root: -*carbosulfan* : 4 x <0.05 mg/kg -*carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: 4 x <0.1 mg/kg **Leaves: -*carbosulfan* : 4 x <0.05 mg/kg -carbofuran + 3-OH-carbofuran expressed as carbofuran equiv.: 4 x <0.1 mg/kg			

[16] Sugar beet data and MRL proposal need to be reviewed in the light of the EPCO 34 discussion.
[17] The rapporteur Member State proposed that the residue values “0.248”, “0.063” and “0.112” should be considered as “outliers” according to the DIXON Q-Test.

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Maize	NE	**grain: -*carbosulfan* : 6 x <0.05 mg/kg -*carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: 6 x <0.1 mg/kg **Whole plant with cobs : -*carbosulfan* : 6 x <0.05 mg/kg -carbofuran + 3-OH-carbofuran expressed as carbofuran equiv.: 6 x <0.1 mg/kg	Samples of plants with cobs (BBCH 18-85) at different PHI's up to normal harvest time and maize grains were analysed for carbosulfan, carbofuran and 3-OH-carbofuran. Decay curves are given with last sampling 160 to 193 days after the application. Trials performed in accordance with the critical GAP	*Carbosulfan* : 0.05* mg/kg *Carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: 0.1* mg/kg	*Carbosulfan* : 0.05* mg/kg *Carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: 0.1* mg/kg
	SE	**grain: -*carbosulfan* : 2 x <0.05 mg/kg -*carbofuran + 3-OH-carbofuran expressed as carbofuran equiv*.: 2 x <0.1 mg/kg **Whole plant with cobs : -*carbosulfan* : 3x <0.05 mg/kg -*carbofuran + 3-OH-carbofuran expressed as carbofuran equiv.: <0.1, 0.11, 0.14 mg/kg*			

(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 critical GAP

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Consumer risk assessment [18] (Annex IIA, point 6.9, Annex IIIA, point 8.8)

a) Carbosulfan

ADI	*0.01mg/kg bw/day*
TMDI [19] (% ADI)	*0.47 % (WHO European diet)* *1.62 % (German model)* *3.56 % and 8.18 % respectively for children and infants from UK. (Pesticides Safety Directorate Consumer Exposure Model).*
IEDI (European Diet) (% ADI)	-
Factors included in NEDI	-
ARfD	*0.01 mg/kg bw/day*
Acute exposure [20] (% ARfD)	*UK PSD model:* *Adults / Toddlers* *Mandarins: 5.4 % / 26.7 %* *Orange fruit: 8.71 % / 39.3 %* *Orange pulp: 8.71 % / 39.3 %* *Orange juice: 3.56 % / 17.37 %* *Sugar beet: 1.03 % / 4.05 %* *Maize grain: 1.84 % / 5.10%*

b) Carbofuran + 3-OH-carbofuran expressed as carbofuran equivalents

ADI	*0.001mg/kg bw/day*
TMDI [21] (% ADI)	*36.41 % (WHO European diet)* *148.37 % (German model)* *350 % and 693 % respectively for children and infants from UK (Pesticides Safety Directorate Consumer Exposure Model).*
IEDI (European Diet) (% ADI)	-
Factors included in IEDI	-

[18] Risk assessment is inconclusive, needs to be finalised upon receipt of further toxicology and residue data
[19] RMS initial assessment considering withdrawn uses on citrus and cotton should not be considered as agreed. No updated chronic assessment available
[20] Calculations not conclusive, RMS presented an updated calculation in an addendum which was not peer reviewed.
[21] RMS initial assessment considering withdrawn uses on citrus and cotton should not be considered as agreed. No updated chronic assessment available.

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ARfD	*0.001mg/kg bw/day*
Acute exposure [22] (% ARfD)	*UK PSD model:* *Adults / Toddlers* *Mandarins: 573 % / 2836 %* *Mandarins pulp 97 % / 481 %* *Orange fruit: 679 % / 3068 %* *Orange pulp: 174 % / 786 %* *Orange juice: 71 % / 347 %* *Sugar beet: 27 % / 81 %* *Maize grain: 37 % / 102 %*

Processing factors [23] (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Commodities	Grapefruits			Oranges		
	Carbosulfan	Carbofuran	3-OH carbofuran	Carbosulfan	Carbofuran	3-OH-carbofuran*
Unwashed whole fruit (RAC)	0.125	0.135	0.32	0.17	0.265	0.295
Transfer factor (RAC/washed fruit)	*<0.4*	*0.77*	*0.92*	*0.47*	*1.28*	*1.35*
Transfer factor (RAC/juice)	*<0.4*	*<0.37*	*<0.15*	*<0.29*	*<0.18*	*<0.17*
Transfer factor (RAC/molasses)	*<0.4*	*1.74*	*2.93*	*<0.3*	*1.56*	*1.27*
Transfer factor (RAC/dried pulp)	*0.8*	*1.11*	*4.0*	*0.9*	*1.15*	*5.62*
Transfer factor (RAC/finisher pulp)	*<0.4*	*<0.37*	*<0.15*	*<0.29*	*<0.18*	*<0.17*
Transfer factor (RAC/oil)	*19.36*	*11.7*	*<0.3*	*7.11*	*14.86*	*0.17*
Remark : The percent of transference couldn't be calculated. * The asterisk refers to "Residues expressed as Carbofuran equivalent/kg" using the conversion factor.						

* Calculated on the basis of distribution in the different portions, parts or products as determined through balance studies

[22] Calculations not conclusive, RMS presented an updated calculation in an addendum which was not peer reviewed
[23] no data on dibutylamine DBA available

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

Expression of the residue	Crops	MRLs (mg/kg)
Carbosulfan	Sugar beet	*0.05**
	Maize	*0.05**
Carbofuran (Carbofuran + 3-OH carbofuran expressed as carbofuran)	Sugar beet	*0.1**
	Maize	*0.1**
Remark: These are provisional MRLs as the residue data bases are incomplete.		

*) LOQ

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Appendix 1.5: Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	0.55-7.3 % after 28-120 d, [^{14}C-phenyl ring]-label (n= 6)
Non-extractable residues after 100 days ‡	34.4-90.3 % after 28-120 d, [^{14}C-phenyl ring]-label (n= 6) 29.9-35.1 % after 28 d, [^{14}C-dibutylamine]-label (n= 2)
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum)	Carbofuran : 34.6-88 % at 7-14 days (n= 6) 3-keto-carbofuran: 6.6 % AR at 28 d (end of the study) Dibutylamine: 15.4-21.5% at 0-3 days (n=2)

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

Anaerobic degradation ‡	No data available
Soil photolysis ‡	No data available, studies performed with metabolite carbofuran show that this metabolite is stable to photolysis in soil.

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

Method of calculation	Laboratory: first-order kinetics Field studies: first order kinetics
Laboratory studies ‡ (range or median, with n value, with r^2 value)	DT_{50lab} carbosulfan (20°C, pF 2.0): **kinetic data needs to be reassessed** No DT_{50} for carbofuran are provided in the carbosulfan DAR. The corresponding box from the carbofuran list of end points is copied here. Please note that some data pertain to a different applicant. (DT_{50}carbofuran (study performed with carbofuran): 15.1, 9.5, 15.8, 19.4 d) (DT_{50}carbofuran (study performed with benfuracarb): 6.1d, 15 d, 7.6 d, 15 d) Note: benfuracarb study is not summarized in the carbofuran DAR but in the benfuracarb one. (Applicant: Dianica) DT_{50lab} (normalized to 20°C, pF2.0, aerobic): 175 d (r^2 = 0.92), 381d (r^2 = 0.98) and 444 d (r^2 not reported) based on studies with carbofuran as parent - Applicant: FMC, only values from acceptable

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	studies) **Overall geometric mean carbofuran DT_{50}:** 29.28d *Degradation data for dibutylamine required*
	DT_{90lab} carbosulfan (20°C, aerobic): *kinetic data needs to be reassessed* DT_{90lab} (20°C, aerobic): 14.52-1465 d, (based on two studies that were performed with benfuracarb (Applicant Dianica) and carbofuran (Applicants Dianica and FMC) as test substance, some values significantly beyond the duration of the study)
	DT_{50lab} (10°C, aerobic): 25.4 d (n= 1, r^2 = not available)
	DT_{50lab} (20°C, anaerobic): No data available.
	Degradation in the saturated zone: no data available, not required.
Field studies ‡ (state location, range or median with n value)	DT_{50f}: carbosulfan, Netherlands, Spain, Italy, UK, bare soil, 0.35-31.3 d (geometric mean 4.6 d, median 7.8 d, n= 6, r^2 =0.88-0.997) 1st order DT_{50f}: carbofuran, Netherlands, Spain, Italy, UK, bare soil, 1.3-71.9 d (mean 22.8 d, median 16.5 d, n= 6, r^2 =0.880-0.997) 1st order DT_{50f}: carbofuran, USA, 5.0 – 121 d (Field studies with carbofuran as parent. Only studies assessed as acceptable and representative of EU conditions by the RMS). **Note: these studies are not summarized in the carbosulfan DAR** **Overall geometric mean:** 20.75 d (no normalization possible with the available data in the summary of the studies).
	DT_{90f}: carbofuran, Netherlands, Spain, Italy, UK, bare soil, 4.4-237.3 (extrapolated) d (n= 6, r^2 =0.880-0.997) 1st order (Field studies were carbosulfan was applied as parent and carbofuran appears as metabolite, FMC) DT_{90f}: carbofuran, USA, 16.5 – 399 d (Field studies with carbofuran as parent. Only studies assessed as acceptable and representative of EU conditions by the RMS).

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Soil accumulation and plateau concentration ‡	No data available

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡ K_d ‡ pH dependence ‡ (yes / no) (if yes type of dependence)	*Data gap identified by EPCO 31*

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

Column leaching ‡	Point covered by a Thin Layer Chromatography study on 4 soils. Relative mobility with respect to reference substances (2,4-D and DDT) has been determined
Aged residues leaching ‡	Study of limited quality available in the DAR
Lysimeter/ field leaching studies ‡	Location: Germany, Lower Saxony, Borstel Study type: 2 lysimeters Number of applications: 1 application Application rate:1.05 kg/ha/year on bare soil Average annual rainfall (mm): 800 mm Average annual leachate volume (mm): 493 mm Annual average concentrations: 0.82-0.85 µg equivalent a.s./L (no information on the leachate concentrations of carbosulfan, carbofuran and possible metabolites)

PEC (soil) (Annex IIIA, point 9.1.3)

PEC soils are required for dibutylamine

PEC formulation Marshal 10 G (granular application in the sowing bed)

Method of calculation	DT_{50} (carbosulfan): 31.3 days Kinetics: 1st order worst case field DT_{50} (worst case FMC study)
Application rate	Crop: maize, sugar beets, sunflower 0% plant interception: granule incorporation in the seed furrow Number of applications: 1 Application rate: 0.75 kg a.s./ha

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PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	1.000	1.000	-	-
Short term 24h	0.978	0.989	-	-
2d	0.957	0.978		
4d	0.915	0.957		
Long term 7d	0.856	0.926	-	-
28d	0.538	0.745		
50d	0.330	0.605		
100d	0.109	0.402		

Metabolite

Method of calculation	DT_{50} (carbofuran): 71.9 days Kinetics: 1st order worst case field DT_{50} (worst case FMC study)
Application rate	Crop: maize, sugar beet, sunflower 0% plant interception: granular application in the sowing bed, soil layer: 5 cm, soil density: 1.5 kg/dm^3 Number of applications: 1 Application rate(s): 437 g/ha (assumed carbofuran is formed at a maximum of 100% of the applied dose, molecular mass of carbosulfan is 380.5; molecular mass of carbofuran is 221.3)

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.583	0.583	-	-
Short term 24h	0.577	0.580	-	-
2d	0.572	0.577		
4d	0.561	0.572		
Long term 7d	0.545	0.563	-	-
28d	0.445	0.511		
50d	0.360	0.462		
100d	0.222	0.374		

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PEC formulation Marshal 25 CS (foliar application in cotton and citrus)

Method of calculation	DT_{50} (carbosulfan): 31.3 days Kinetics: 1st order worst case field DT_{50} (worst case FMC study)
Application rate	Crop: cotton 50% plant interception: spray application soil layer: 5 cm, soil density :1.5 kg/dm^3 Number of applications: 2 with an interval of 14 days Application rate: 0.375 kg a.s./ha

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.250	0.250	0.433 max conc. after 2nd application	-
Short term 24h	0.245	0.247	-	-
2d	0.239	0.245		
4d	0.229	0.239		
Long term 7d	0.214	0.232	-	-
28d	0.134	0.186		
50d	0.083	0.151		
100d	0.027	0.101		

Metabolite

Method of calculation	DT_{50} (carbofuran): 71.9 days Kinetics: 1st order worst case field DT_{50} (worst case FMC study)
Application rate	Crop: cotton 50% plant interception: spray application soil layer: 5 cm, soil density :1.5 kg/dm^3 Number of applications: 2 with an interval of 14 days Application rate: 0.218 kg a.s./ha (assuming carbofuran is formed at a maximum of 100% of the applied dose, molecular mass of

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	carbosulfan is 380.5; molecular mass of carbofuran is 221.3)

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.145	0.145	0.272 max conc. after 2nd application	-
Short term 24h 2d 4d	0.144 0.143 0.140	0.145 0.144 0.143	-	-
Long term 7d 28d 50d 100d	0.136 0.111 0.090 0.055	0.141 0.127 0.115 0.093	-	-

Method of calculation	DT_{50} (carbosulfan): 31.3 days Kinetics: 1st order worst case field DT_{50} (worst case FMC study)
Application rate	Crop: citrus 50% plant interception: spray application soil layer: 5 cm, soil density :1.5 kg/dm^3 Number of applications: 2 with an interval of 14 days Application rate: 0.75 kg a.s./ha

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.500	0.500	0.867 max conc. after 2nd application	-
Short term 24h 2d 4d	0.489 0.478 0.458	0.495 0.489 0.478	-	-

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$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Long term 7d	0.428	0.463	-	-
28d	0.269	0.373		
50d	0.165	0.302		
100d	0.055	0.201		

Metabolite

Method of calculation	DT_{50} (carbofuran): 71.9 days Kinetics: 1st order worst case field DT_{50} (worst case FMC study)
Application rate	Crop: <u>citrus</u> 50% plant interception: spray application soil layer: 5 cm, soil density :1.5 kg/dm^3 Number of applications: 2 with an interval of 14 days Application rate: 0.436 kg a.s./ha (assuming carbofuran is formed at a maximum of 100% of the applied dose, molecular mass of carbosulfan is 380.5; molecular mass of carbofuran is 221.3)

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.291	0.291	0.545 max conc. after 2nd application	-
Short term 24h	0.288	0.289	-	-
2d	0.285	0.288		
4d	0.280	0.285		
Long term 7d	0.272	0.281	-	-
28d	0.222	0.255		
50d	0.179	0.231		
100d	0.111	0.187		

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Hydrolysis of active substance and relevant metabolites (DT_{50}) ‡ (state pH and temperature)	pH5: 25°C DT_{50} 0.2 hr (1st order) Major hydrolysis products : Carbofuran and dibutylamine; carbofuran decomposes to 7-phenol under basic conditions pH7: 20°C 11.4 hr (1st order) distilled water (pH 7.3) : DT_{50} = 18.2 hr (1st order) pH9: 20°C DT_{50} 173.3 hr (ca 7 d) (1st order)
Photolytic degradation of active substance and relevant metabolites ‡	Not available - required
Readily biodegradable (yes/no)	No, 28% biodegradation after 28 days
Degradation in water/sediment - DT_{50} water ‡ - DT_{90} water ‡ - DT_{50} whole system ‡ - DT_{90} whole system ‡	 1.3-1.8 days 4.3-6.1 days (1st order, r^2=0.85-1.00, n= 3) 4.2-5.4 days 13.8-17.9 days (1st order, r^2= 0.85-0.98, n= 3)
Mineralization	20.00-30.38 %AR (at 102 d, study end, n= 3)
Non-extractable residues	30.53- 42.99% AR (at 102 d, study end, n= 3)
Distribution in water / sediment systems (active substance) ‡	Maximum of 17.61-32.03 %AR in sediment after 2-7days. DT_{50} in sediment =DT_{50} whole system
Distribution in water / sediment systems (metabolites) ‡	Water: Carbofuran : max of 24.36-33.24% (7-14 days, n= 3); DT_{50} = 18.9-23.2 d (n=2) 7-phenol : max of 1.35-11.66 % (1-7days, n= 3) Sediment: Carbofuran : max of 11.76-20.09% (0.25-14 days, n= 3); DT_{50} = 20.0-21.8 d (n=2) Unknown 3: max of 11.57-16.53 % (0.25-2 days, n= 2)

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

Parent (carbosulfan)

MARSHAL 10 G (granule incorporation)

Method of calculation	*FOCUS SW required*

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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Application rate	Crop: maize, sugar beets 0% plant interception: granule incorporation in the seed furrow, soil Number of applications: 1 Application rate: 0.75 kg a.s./ha => 0.436 kg carbofuran/ha (assuming conversion for respective molar weights)
Main routes of entry	Drainage, run off

MARSHAL 25 CS (foliar application)

Parent (carbosulfan)

Method of calculation	*FOCUS SW required*
Application rate	Crop: cotton 60% plant interception: spray application No of appl.: 2 with an interval of 14 days Application rate: 0.375 kg a.s./ha
Main routes of entry	Drift, run off and erosion

Parent (carbosulfan)

Method of calculation	*FOCUS SW required*
Application rate	Crop: citrus 30% plant interception: spray application No of appl.: 2 with an interval of 14 days Application rate: 0.75 kg a.s./ha
Main routes of entry	Drift, run off and erosion

The PEC surface water should be revised considering the FOCUS recommendations.

PEC (sediment)

The PEC sediment should be revised considering the FOCUS recommendations.

PEC (ground water) (Annex IIIA, point 9.2.1)

DT_{50} in soil needs to be reassessed and a data gap has been identified for Koc. PEC groundwater should be calculated for the active substance and the metabolites with more adequate endpoints.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	Not studied - no data requested
Photochemical oxidative degradation in air ‡	DT_{50} of 2.0 hours derived by the Atkinson method of calculation
Volatilization ‡	**Studies available in the dossier, not summarized in the DAR.**

PEC (air)

Method of calculation	Expert judgment, based on vapour pressure, dimensionless Henry's Law Constant and information on volatilisation from plants and soil.

$PEC_{(a)}$

Maximum concentration	Not required

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	**Soil** Definitions for risk assessment: carbosulfan, carbofuran, 3-keto-carbofuran and dibutylamine. Definitions for monitoring: carbosulfan, carbofuran, 3-keto-carbofuran (included pending the finalization of the risk assessment) **Water** **Ground water** Definitions for exposure assessment: carbosulfan, carbofuran, 3-keto-carbofuran and dibutylamine. Definitions for monitoring: carbosulfan, carbofuran, 3-keto-carbofuran and dibutylamine (all compounds included pending the finalization of the assessment) **Surface water** Definitions for risk assessment: carbosulfan (water and sediment), carbofuran (water and sediment), carbofuran-7-phenol (only water phase), dibutylamine (partition properties in water sediment not known). Definitions for monitoring: carbosulfan, carbofuran

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study)	Not available
Ground water (indicate location and type of study)	Not available
Air (indicate location and type of study)	Not available

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	Candidate for R53 May cause long-term adverse effect to the aquatic environment

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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Appendix 1.6: Effects on non-target Species

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

Acute toxicity to mammals ‡ Reproductive toxicity to mammals	LD_{50} = 42.7 mg/kg bw/d (rabbit) NOAEL = 20 ppm (1.2 mg/kg bw/d); Reduced number born pups at parental toxic doses (rat)
Acute toxicity to birds ‡ Acute toxicity to birds (MARCHAL 25 CS)	LD_{50} = 10 mg a.s./kg b.w. NOEL (based on mortality) = 2.51 mg a.s./kg b.w. (mallard duck) LD_{50} = 8-16 mg/kg bw
Dietary toxicity to birds ‡	LC_{50} = 3.99 mg a.s./kg b.w./day (mallard duck)
Reproductive toxicity to birds ‡	NOEL = 30 mg a.s./kg feed or 2.5 mg a.s./kg b.w./day (mallard duck)

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

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger
0.75 kg a.s./ha, 2 appl. with an interval of 14 d	citrus	Small herbivorous mammal	Acute	0.4	10
			Long term	0.03	5
0.375 kg a.s./ha, 2 appl. with an interval of 14 d	cotton	Medium herbivorous mammal	Acute	3.9	10
			Long term	0.4	5
0.75 kg a.s./ha, 2 appl. with an interval of 14 d	citrus	Insectivorous bird	Acute	0.2	10
			Short term	0.2	10
			Long term	0.11	5
0.375 kg a.s./ha, 2 appl. with an interval of 14 d	cotton	Medium herbivorous bird	Acute	0.5	10
			Short term	0.5	10
			Long term	0.3	5
		Insectivorous bird	Acute	0.5	10
			Short term	0.4	10
			Long term	0.2	5

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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MARSHAL 10 G (granule use)

LD_{50}, LC_{50}, NOEL expressed in number of granules for different sizes of birds

Time scale	Number of granules for a 15 g bird	Number of granules for a 50 g bird	Number of granules for a 200 g bird	Number of granules for a 500 g bird
Acute LD_{50}	11	36	143	357
Acute NOEL for mortality	3	9	36	90
Dietary LC_{50}	4	14	57	143
NOEL reproduction	3	9	36	90

LC_{50}, NOEL expressed in number of granules for different sizes of mammals

Time scale	Number of granules for a 10 g mammal	Number of granules for a 25 g mammal	Number of granules for a 100 g mammal
Acute LD_{50}	30.5	76	305
NOAEL reproduction	1	2	9

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	Endpoint	Toxicity (mg/L)
Laboratory tests ‡				
Lepomis macrochirus	carbosulfan	96 h	Mortality, LC_{50}	0.015
Oncorhynchis mykiss		14 d	Prolonged tox, NOEC	0.003
Daphnia magna		48 h	Mortality, EC50	0.0015
Daphnia magna		21 d	Reproduction, NOEC	0.0032
Scenedesmus subspicatus		96 h	EC_{50}	> 20
Oncorhynchus mykiss	carbofuran	96 h	EC_{50}	0.3625 (*)
Cyprinodon variegatus		35 d	early life stage, NOEL	0.006
Daphnia magna		48 h	Mortality, EC50	0.0386
Ceriodaphnia dubia		7 d	Mortality, NOEC	0.00016
Oncorhynchis mykiss	7-phenol	96 h	Mortality, LC_{50}	37
Daphnia magna		48 h	Mortality, EC50	30
Selenastrum capricornutum		72 h	E_bC_{50} E_rC_{50}	47 83

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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Group	Test substance	Time-scale	Endpoint	Toxicity (mg/L)
Oncorhynchis mykiss	dibutylamine	96 h	Mortality, LC_{50}	18
Daphnia magna		48 h	Mortality, EC50	4.2
Selenastrum capricornutum		72 h	E_bC_{50} E_rC_{50}	24 31
Daphnia magna	MARSHAL 25CS	48 h	Mortality, EC50	0.0043
Selenastrum capricornutum		72 h	E_bC_{50} E_rC_{50}	429 805
Daphnia magna		48 h	Mortality, EC50	0.01

*: the most critical endpoint for fish is *Lepomis macrochirus*, 96 h semi-static, LC_{50} = 0.18 mg a.s./L, Migchielsen M.H.J., 2002 (Dianica)

Microcosm or mesocosm tests
Outdoor mesocosm containing aquatic invertebrates, algae and macrophytes, 1 application, the test item is MARSHAL 25 CS (capsule suspension containing 250 g/L carbosulfan) *A reevaluation of the study is pending.*

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

TER carbosulfan (foliar use) based on spray drift

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
0.375 kg a.s./ha, 1 appl.	Cotton	*Lepomis macrochirus*	96 h	1	**4.4**	100
				20	**80**	100
				30	120	100
		Daphnia magna	48 h	1	**0.4**	100
				20	**8.0**	100
				30	**12.0**	100
		S. subspicatus.	96 h	1	5899	10
				20	106667	10
				30	160000	10
		Oncorhynchis mykiss	14 d	1	**0.9**	10
				20	16.0	10
				30	24.0	10
		Daphnia magna	21 d	1	**0.9**	10
				20	17.1	10
				30	25.6	10

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Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
0.0375 kg a.s./hl (or max 0.75 kg a.s./ha), 1 late appl.	citrus	*Lepomis macrochirus*	96 h	3	**0.4**	100
				20	**5.5**	100
				50	**27.3**	100
		Daphnia magna	48 h	3	**0.0**	100
				20	**0.6**	100
				50	**2.7**	100
		S. subspicatus.	96 h	3	508.6	10
				20	7339	10
				50	36363	10
		Oncorhynchis mykiss	14 d	3	**0.1**	10
				20	**1.1**	10
				50	**5.5**	10
		Daphnia magna	21 d	3	**0.1**	10
				20	**1.2**	10
				50	**5.8**	10

TER carbofuran (metabolite of carbosulfan) (granular and foliar use)

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
No agreed assessment available pending revised PEC_{sw} based on $FOCUS_{sw}$ modelling						

Bioconcentration

Bioconcentration factor (BCF) ‡	990 (whole fish), fillet (730), 1100 (viscera)
Annex VI Trigger:for the bioconcentration factor	100
Clearance time (CT_{50}) (CT_{90})	K_2 (day^{-1}) = 0.087 (fillet) K_2 (day^{-1}) = 0.143 (viscera) -
Level of residues (%) in organisms after the 14 day depuration phase	At the end of the 30 day depuration period, 60%, 72% and 72% of the accumulated residues were eliminated from the fillet, viscera and whole fish respectively

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Acute oral toxicity ‡	LD_{50} (48h, carbosulfan) 0.18 µg a.s./bee
Acute contact toxicity ‡	LD_{50} (48h, carbosulfan) 1.035 µg a.s./bee

Acute oral toxicity ‡	LD_{50} (48h, carbofuran) : not available
Acute contact toxicity ‡	LD_{50} (48h, carbofuran) 0.038µg a.s./bee

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
0.75 kg a.s./ha	Maize, sugar beet	Oral	Not applicable	-
		Contact	Not applicable	-
0.375 kg a.s./ha	cotton	Oral	**362.3**	50
		Contact	**2083.3**	50
0.75 kg a.s./ha	citrus	Oral	**724.6**	50
		Contact	**4166.7**	50

a.s.: carbosulfan

Field or semi-field tests
Carbosulfan was applied to blooming seed alfalfa by fixed-wing aircraft to determine the effects on honeybees. The formulations EC 25 g/L and EC 40 g/L were applied at the rate of 0.56 and 1.12 kg a.s./ha. The carbosulfan treatments were classified as highly toxic to bees for 2-3 days. The study is of limited quality.

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

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect	Annex VI Trigger
Laboratory tests ‡						
Typhlodromus pyri	protonymphs	carbosulfan	0.12 kg a.s./ha	mortality	96%	30%
Aphidius rhopalosiphi	Adult wasps	carbosulfan	0.12 kg a.s./ha	mortality	100%	30%

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect	Annex VI Trigger
Poecilus cupreus	adult beetles	carbosulfan	0.12 kg a.s./ha	mortality feed consumption	76.7% no effect	30%
Pardosa sp.	Adult spiders	carbosulfan	0.12 kg a.s./ha	mortality	100%	30%
Pardosa sp.	Adult spiders	MARSHAL 25EC	0.375 kg a.s./ha	mortality	100%	30%
Semi-field test						
Pardosa sp.	Adult spiders (small potato field enclosure)	MARSHAL 25EC	0.375 kg a.s./ha	mortality	100% after 24 h 52.5% after 5 days (for the newly introduced spiders)	

Field or semi-field tests						
Pardosa sp.	Adult spiders (small potato field enclosure)	MARSHAL 25EC	0.375 kg a.s./ha	mortality	100% after 24 h 52.5% after 5 days (for the newly introduced spiders)	

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity ‡	Carbosulfan: not available
Reproductive toxicity ‡	Carbosulfan: not available

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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Field or semi-field tests
The product MARSHAL 25 CS was applied on grassland at the rate of 5.2L/ha (equivalent to 1.3 kg a.s./ha). The absence of detailed information on the soil sampling technique (sampling depth and on crop interception) in the soil does not allow to easily extrapolate the results of the study to other crop scenarios. The average actual concentrations in the soil at day 0 were **0.6** mg/kg wet soil and **2.8** mg/kg wet soil, respectively for carbosulfan and carbofuran. Reduction of earthworm populations (number of adult earthworms, biomass) were observed in the carbosulfan treatment plots 1 month after application. Recovery was observed 6 months and 12 months after application.

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger
The risk assessment is based on a field study.				

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization ‡	No acceptable study with carbosulfan
Carbon mineralization ‡	No acceptable study with carbosulfan
Nitrogen mineralization ‡ (carbofuran)	No effect after 28 days at the application rates of 16 and 80 mg Furadan 5 G/kg soil (0.8 and 4 mg carbofuran/kg soil)
Carbon mineralization ‡ (carbofuran)	No effect after 28 days at the application rates of 16 and 80 mg Furadan 5 G/kg soil (0.8 and 4 mg carbofuran/kg soil)

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	N Dangerous for the environment R50/53 Very toxic for aquatic organisms, may cause long-term adverse effects to the aquatic environment

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
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
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
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

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LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
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
NOEC	no observed effect concentration
NOEL	no observed effect level
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
PHED	pesticide handler's exposure data
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
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

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