CONCLUSION ON PESTICIDES PEER REVIEW

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# Peer review of the pesticide risk assessment of the active substance dimethoate

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## Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State Italy and co-rapporteur Member State Bulgaria for the pesticide active substance dimethoate are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of dimethoate as insecticide on wheat and sugar beet. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.



**Keywords:** Dimethoate, peer review, risk assessment, pesticide, insecticide

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## Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Dimethoate is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), Italy, and co-rapporteur Member State (co-RMS), Bulgaria, received an application from Cheminova for the renewal of approval of the active substance dimethoate. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Bulgaria), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on dimethoate in the renewal assessment report (RAR), which was received by EFSA on 5 May 2017. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Cheminova, for comments on 7 June 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 8 August 2017.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether dimethoate can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of dimethoate as insecticide on wheat and sugar beet, as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the use of dimethoate results in a sufficient insecticidal efficacy against the target organisms according to the representative uses proposed at EU level.

A data gap was identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites with specific regards to the reporting and evaluation of the collected literature data.

In the area of identity, physical chemical properties and analytical methods a data gap for a monitoring method for dimethyldithiophosphate (Met XV) in body fluids was identified.

In the area of mammalian toxicology, data gaps were identified for an assessment of the toxicological relevance of the individual impurities present in the technical specification in comparison with the toxicological profile of the parent compound; for clarification of the gene mutation potential with robust *in vivo* follow-up to the positive mutagenic effects observed in bacterial and mammalian cells *in vitro* with dimethoate and for the clarification of the endocrine-disrupting potential of dimethoate, in particular regarding the thyroid pathway in mammals (issue not finalised). Critical areas of concern were identified since positive gene mutation effects were observed in bacterial and mammalian cells *in vitro* with dimethoate that were not adequately followed up with *in vivo* studies. Since a mutagenic potential could not be excluded for dimethoate, no threshold for these effects is assumed and therefore toxicological reference values could not be established. Non-dietary exposure risk assessment could not be conducted. The omethoate metabolite was concluded to be an *in vivo* mutagen. In addition, the technical specification (either the current or the revised one) is not supported by the toxicological assessment.

In the area of residues, several data gaps were identified for storage stability data for dimethoate and omethoate in cereal straw and for additional Good Agricultural Practice (GAP)-compliant residue trials on sugar beet and analysing for dimethoate and omethoate residues. Most notably, since a mutagenic potential could not be excluded for dimethoate, toxicological reference values could not be established and a dietary risk assessment for the consumers could not be conducted. Furthermore, since omethoate was concluded to be an *in vivo* mutagen, the setting of toxicological reference values for this metabolite is not considered appropriate. This leads to a critical area of concern.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at the European Union (EU) level. A data gap was identified for information on the effect of water treatment processes on the nature of residues of the active substance and metabolites omethoate and *O*-desmethyl dimethoate (Met X) potentially present in

surface, when surface water or groundwater are abstracted for drinking water. This gap leads to the fact that the consumer risk assessment from the consumption of drinking water could not be finalised for all the representative uses.

In the area of ecotoxicology, several data gaps were identified. The risk assessment for birds could not be finalised. Critical areas of concern were identified for mammals, bees and non-target arthropods, for which a high risk has been concluded.

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## Background

Commission Implementing Regulation (EU) No 844/2012[1] (hereinafter referred to as 'the Regulation') lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009.[2] This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS Italy and co-RMS Bulgaria received an application from Cheminova for the renewal of approval of the active substance dimethoate. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Bulgaria), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on dimethoate in the RAR, which was received by EFSA on 5 May 2017 (Italy, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Cheminova, for consultation and comments on 7 June 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 8 August 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA, the RMS and the European Commission on 19 September 2017. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in September 2018.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative use of dimethoate as an insecticide on wheat and sugar beet, as proposed by the applicant. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2018), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

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

the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (19 September 2017);
- the evaluation table (25 September 2018);
- the report(s) of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Italy, 2018), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

## The active substance and the formulated product

Dimethoate is the ISO common name for *O*,*O*-dimethyl *S*-methylcarbamoylmethyl phosphorodithioate or 2-dimethoxyphosphinothioylthio-*N*-methylacetamide (IUPAC).

The representative formulated product for the evaluation was 'CHA 3621-04', an emulsifiable concentrate (EC) containing 400 g/L dimethoate.

The representative uses evaluated were spray applications on sugar beet, turnip and beetroot for the control of aphids and leaf miner and on cereals (wheat, rye, triticale, durum wheat) against leaf and ear aphids in the European Union (EU). Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the use of dimethoate according to the representative uses proposed at EU level results in a sufficient insecticidal efficacy against the target organisms, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b)

A data gap has been identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on health, the environment and non-target species and published within the 10 years before the date of submission of the dossier. Specifically, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

## Conclusions of the evaluation

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

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The proposed specification for dimethoate was based on batch data from industrial scale production. The proposed minimum purity of the technical material is 970 g/kg. Omethoate and isodimethoate were considered relevant impurities with maximum contents of 1 g/kg and 3 g/kg, respectively. It should be noted that the evaluation of the toxicological relevance of the other impurities was not finalised (see data gap in Section 2). The manufactured technical material meets the requirements of the existing FAO specification under the new procedure 59/TC (May 2005) of minimum 950 g/kg dimethoate content, referring to the material of Cheminova A/S. It meets also the requirement of the specification concerning the relevant impurities of maximum 2 g/kg omethoate and max. 3 g/kg isodimethoate content. The batches used in the (eco)toxicological assessment do not support the current reference specification and the proposed revised specification (See Sections 2 and 5).

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 dimethoate or the representative formulation. The main data regarding the identity of dimethoate and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of dimethoate in the technical material and in the representative formulation, and for the determination of the relevant impurities in the technical material and formulation.

Residues of dimethoate and omethoate in food and feed of plant origin can be monitored by the QuEChERS multi-residue method using high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) with limit of quantifications (LOQs) of 0.01 mg/kg for both analytes, in all commodity groups. A QuEChERS method using HPLC–MS/MS exists for analysis of dimethoate and omethoate with LOQs of 0.001 mg/kg for both analytes in bovine milk, bovine fat, liver, kidney, muscle and poultry egg. However, it should be noted that both residue definitions in food/feed from plant origin and in food of animal origin were set as provisional (See Section 3).

Dimethoate and omethoate residues in soil can be monitored by gas chromatography with flame photometric detector (GC-FPD) or HPLC–MS/MS with LOQs of 0.01 mg/kg for both analytes. An appropriate HPLC–MS/MS method exists also for the determination of omethoate in soil with a LOQ of 0.005 mg/kg. Dimethoate and omethoate residues in drinking water can be monitored by gas chromatography with mass spectrometry (GC–MS) with LOQs of 0.05 μg/L for both analytes, while the HPLC–MS/MS method exists for monitoring both compounds in tap water and surface water with LOQs of 0.05 μg/L. Dimethoate and omethoate residues in air can be determined by GC-FPD with LOQs of 0.01 $\mu g/m^3$ for each analyte. The QuEChERS multi-residue method using HPLC–MS/MS can be used for the analysis of dimethoate, omethoate and dimethoate carboxylic acid in body fluids with LOQs of 0.01 mg/L for each compound. However, it should be noted that the residue definition for body fluids was established as dimethoate, omethoate, dimethyldithiophosphate (Met XV) and dimethoate carboxylic acid (Met III) (See Section 2) as a consequence, a data gap for monitoring method for dimethyldithiophosphate (Met XV) in body fluids was identified.

## 2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012), Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products (EFSA, 2014b) and Guidance on the Application of the CLP Criteria (ECHA, 2017).

Dimethoate was discussed at the Pesticides Peer Review Experts' Meeting 178 in April 2018.

Both the current and the revised technical specifications are not supported by the batches used in the toxicity studies. Although the revised technical specification has a lower level of impurities, relevant impurities such as omethoate (mutagenic *in vivo* – see below) and isodimethoate (both impurities having a higher acetylcholinesterase (AChE) inhibition potential than dimethoate) were considered not sufficiently tested. Accordingly, a critical area of concern was identified. The toxicological relevance of the individual impurities present in the technical specification has not been addressed in comparison with the toxicity profile of the parent compound, except for the known relevant impurities (data gap). The analytical methods used in the toxicological studies were considered fit-for-purpose in the overall toxicological data package.

In rat, dimethoate is rapidly and extensively absorbed after oral administration, it is widely distributed, metabolised and mainly excreted via the urine. A residue definition for body fluids and tissues was established for dimethoate, omethoate, dimethyldithiophosphate (Met XV) and dimethoate carboxylic acid (Met III); the latter two being identified as major metabolites in rat urine. An *in vitro* interspecies comparative metabolism study supported by human *in vivo* data did not evidence the occurrence of any unique human metabolite.

High acute toxicity was observed when dimethoate was administered by the oral route, while the acute toxicity was low to moderate when dimethoate was administered by the dermal or inhalation routes. No skin irritation or skin sensitisation potential was attributed to the active substance; however, dimethoate was irritant to the eyes. The resulting proposed classification[3] according to Regulation (EC) No 1272/2008[4] (CLP Regulation) criteria includes Acute Tox. 3, H301 'Toxic if swallowed' (while

[3] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

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

harmonised classification refers to Acute Tox. 4, H302), Acute Tox. 4, H332 'Harmful if inhaled' and Eye Irrit. 2, H319 'causes serious eye irritation' (no harmonised classification regarding these two endpoints). Dimethoate does not absorb light above 290 nm and therefore no phototoxicity or photomutagenicity studies are required.

AChE inhibition in erythrocytes (red blood cells (RBC)) and in brain is the most sensitive toxicological endpoint for dimethoate, following short- and long-term exposure either via the oral or dermal routes in all species tested (rat, dog and mouse). The relevant short-term and long-term no-observed-adverse-effect levels (NOAELs) are 0.06 and 0.04 mg/kg body weight (bw) per day, respectively, observed in the 90-day interim and terminal sacrifice in the 2-year study in rat. A potential carcinogenicity effect could not be excluded in rats, based on a small increased incidence over controls in brain granular cell tumours; however, no carcinogenic effects were observed in mice.

A genotoxicity concern was identified from positive results in *in vitro* gene mutations studies in bacterial and mammalian cells. Although some of the studies were not performed according to the current standards, appropriate follow-up testing of dimethoate *in vivo* was not conducted (data gap). Positive *in vitro* results for the end-point chromosome aberrations (CA) were followed by *in vivo* testing showing negative results. Eventually, all experts agreed that a genotoxic potential cannot be excluded for dimethoate (critical area of concern).

Adverse effects were observed on reproductive performance endpoints (reduced pregnancy rate, effects on male reproductive organs) and offspring's development (increased mortality) in rats and mice, though these effects were observed at parental toxic doses (inhibition of RBC and brain AChE activity). In a developmental toxicity study in rats, skeletal abnormalities were observed. Although these effects were observed at maternally toxic doses, the experts considered that classification as Rear. 2 (H361d 'Suspected of damaging the unborn child') may be appropriate. This proposed classification is also supported by a developmental neurotoxicity study in rats showing higher sensitivity of the pups (reduced pup survival with as NOAEL of 0.1 mg/kg bw per day) in the absence of maternal toxicity – the maternal NOAEL in this study was 0.5 mg/kg bw per day based on AChE inhibition. Harmonised classification does not include classification regarding developmental toxicity but it is unknown to EFSA whether the studies considered during the peer review were available to the experts assessing dimethoate classification regarding the human health entry in Annex VI of Reg. 1272/2008. No evidence of immunotoxicity was seen in a 28-day study. Dimethoate is proposed to be classified as toxic for reproduction category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, and toxic effects on the endocrine organs have been observed in the available database (effects on male reproductive organs); therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine-disrupting properties may be met. Mechanistic data are available from the US EPA ToxCast programme indicating that dimethoate does not bind to oestrogen or androgen receptors, is negative in a steroidogenesis assay and is not an aromatase inhibitor. Considering that clear overt systemic toxicity was observed at doses producing the adverse effects on reproductive organs, the experts concluded that, on weight of evidence, dimethoate is unlikely to be an endocrine disruptor. The RMS revised the conclusion after the experts meeting by taking into consideration the US EPA conclusion, indicating that an interaction of dimethoate with the thyroid pathway in mammals and wildlife cannot be excluded. However, in EFSA's view, the experts may not have had the full information available to conclude, and a data gap has been included to address the endocrine-disrupting potential of dimethoate; therefore, this issue could not be finalised.

Most of the available epidemiological studies are indicating effects general to organophosphate pesticides but the studies were not specific for dimethoate. These studies indicate an association between organophosphates and developmental neurotoxicity (DNT) (a biological plausible link is possible but causality cannot be established). In addition, it was noted that the epidemiological studies do not allow for a quantitative risk assessment. Therefore, for risk assessment, the experts agreed that the reference values for dimethoate should be derived from animal studies; and an additional uncertainty factor (UF) of 10 should be applied to account for this additional concern. For the hazard assessment, the experts were, however, considering that due to lack of specific epidemiological data on dimethoate, category 1A/1B for DNT classification could not be proposed.

A number of toxicological studies (acute, genotoxicity, short-term toxicity, comparative AChE inhibiting potential and reproductive/developmental toxicity screening tests) have been provided for the metabolites relevant to consumer exposure, i.e. metabolites **III, X, XI, XII, XX** and **XXIII**. Toxicological reference values were set for these metabolites and reported in the Appendix A. They were all considered of lower toxicity than the parent dimethoate. No toxicological data are available on

the metabolite **XVII** (*O*,*O*-dimethyl phosphoric acid); however, this metabolite is not expected to present cholinesterase activity or to be relevant when compared to the dimethoate toxicological profile. For the relevant metabolite **omethoate**, an almost complete toxicological dossier is available. Omethoate is a more potent AChE inhibitor than dimethoate. The metabolite presents a higher acute toxicity by the oral, dermal and inhalation routes that would require classification[3,4] as Acute Tox. 2 'Fatal if swallowed, in contact with skin and if inhaled' according to the CLP Regulation criteria (although not in line with the current harmonised classification). The relevant short- and long-term NOAELs of omethoate are 0.08 and 0.03 mg/kg bw per day, respectively, derived from the rat studies. No carcinogenic potential has been observed in either rats or mice. *In vitro* positive gene mutation tests in bacterial and mammalian cells were reproduced *in vivo* in a mouse spot test, while positive chromosomal aberration test *in vitro* were adequately contravened by negative chromosomal aberration tests *in vivo*. On this basis, the majority of experts considered omethoate an *in vivo* mutagenic agent. Omethoate produced reduced mating and fertility, as well as reduced pup weight and increased post-natal losses in the presence of parental toxicity (inhibition of RBC and brain AChE activity) in rat. Developmental toxicity consisted of reduced foetal weight in rats and malformations and reduced gravid uterine weights in rabbits; also, these effects were observed in the presence of maternal toxicity. Considering that omethoate showed genotoxic potential *in vivo,* setting of reference values is not considered appropriate (critical area of concern).

Taking into consideration that a genotoxic potential could not be ruled out for dimethoate and that no threshold can therefore be assumed, no toxicological reference values (dietary, such as an acceptable daily intake (ADI) and an acute reference dose (ARfD) or non-dietary, such as an acceptable operator exposure level (AOEL) and an acute acceptable operator exposure level (AAOEL)) can be derived. This represents a critical area of concern. It is noted that the experts discussed the point of departure (PoD) for hypothetical toxicological reference values assuming that the genotoxic potential would have been excluded. Based on the revision of the toxicological profile of dimethoate, even in the case of exclusion of genotoxicity, the existing reference values would not be applicable. The most sensitive PoD was considered to be the DNT NOAEL of 0.1 mg/kg bw per day applying an UF of 1,000 to account for the additional uncertainties highlighted in the epidemiological studies. The resulting value of 0.0001 mg/kg bw (per day) would be relevant for all toxicological reference values[5] (chronic, subchronic, acute, dietary and no-dietary – no correction being needed regarding the oral absorption).

Since non-dietary toxicological reference values were not established, the exposure risk assessment for operators, workers, bystanders and residents cannot be calculated. This leads to a critical area of concern.

Regarding the search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, even though a number of published studies have been assessed and included in the RAR, an assessment of the literature search provided by the applicant has not been performed (data gap).

## 3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of residue chemistry studies (OECD, 2009), the OECD publication on MRL calculations (OECD, 2011), the European Commission guideline document on MRL setting (European Commission, 2011) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Dimethoate was discussed at the Pesticides Peer Review Experts' Meeting 176 in April 2018.

The metabolism was investigated upon foliar application of $^{14}$C-dimethoate labelled on both of the methoxy groups in potatoes, wheat and olives, addressing the three crop categories of root crops, cereals and fruit crops. In all crops at harvest, dimethoate was shown to be extensively degraded into numerous metabolites and was observed predominantly in potato leaves and the green parts of wheat just after application (up to 68% total radioactive residue (TRR) and 97.5% TRR, respectively). Dimethoate and omethoate were detected at trace levels in potato tubers and in wheat grain and were identified at very low levels in wheat straw (3.4–6.2% TRR) and in green and black olives (0.4–2.5% TRR). In all crops at harvest, metabolite **XXIII** was the predominant compound of the TRRs in potato

[5] The current ADI is 0.001 mg/kg bw per day; the ARfD is 0.01 mg/kg bw; the AOEL is 0.001 mg/kg bw per day (EFSA, 2006; European Commission, 2006).

tuber (46.7% TRR), in wheat, whole plant, (26.5% TRR), in wheat grain and straw (up to 47% TRR, respectively) and in olive fruits (green and black) (up to 60% TRR). In addition, the metabolites **XX** and **XI** were recovered in significant proportions in potato tuber only (12% TRR and 15% TRR, respectively) whilst in the different wheat plant parts the metabolite **XII** accounted for up to 30% TRR in the whole green plant, 20% TRR in straw and 11% TRR in grain. All the other identified metabolites (**III**, **IX**, **XV**, **V-conjugates**, **X**) were recovered in much lower proportions (from < 1% to max. 8% TRR).

Dimethoate, omethoate and metabolites **X, XVI** and **XVII** exhibited low and very low persistence in soil which was confirmed in the confined rotational crops metabolism study conducted at the representative plant-back intervals (PBIs) of 30 and 120 days in lettuces, turnips and wheat after a bare soil application of 0.56 kg a.s./ha (2.8 N rate). Transfer of residues from soil into crops was limited as for total residue of < 0.05 mg/kg in the mature crops at 30-day PBI and ranged between < 0.01 mg/kg and 0.02 mg/kg at 120-day PBI. Although further identification of residues in rotational crops was not conducted, residue levels in rotational crops are expected to be below 0.01 mg/kg when the primary crops are treated according to the representative uses.

The effects of processing on the nature of dimethoate and omethoate residues have been investigated at test conditions representing pasteurisation, boiling, baking and brewing and sterilisation. Dimethoate and omethoate were stable to hydrolysis under conditions simulating pasteurisation whilst significant formation of metabolite **X** (28–59.5% of applied radioactivity (AR)) for dimethoate and of metabolites **XI** (36–62% AR) and metabolite **XVII** (19% AR) for omethoate was observed under brewing, baking, boiling and sterilisation conditions. A specific residue definition for processed commodities is not proposed as metabolites X and XI were concluded to be of lower toxicity compared to dimethoate and metabolite XVII is not expected to present a cholinesterase activity or to be relevant when compared to the dimethoate toxicological profile (see Section 2); the definition for primary crops is therefore applicable. Processing residue trials on wheat were submitted and showed a slight concentration of dimethoate and omethoate residues in wheat bran only.

Since the predominant metabolites identified in primary crops and in processed commodities: **XXIII, XX, XI, XII, X** and **XVII** were concluded to be of lower toxicological relevance compared to dimethoate, these compounds were not considered in the dietary risk assessment. Although present at very low levels in wheat grain and sugar beet root (< 0.01 mg/kg), residues of dimethoate and omethoate were found at significant concentrations in wheat straw (up to 0.83 and 0.06 mg/kg, respectively) and omethoate in sugar beet tops and leaves (0.02 mg/kg). The peer review could, however, not conclude on definitive plant residue definitions for enforcement and risk assessment, as a mutagenic potential could not be ruled out for dimethoate, and omethoate is concluded to be mutagenic *in vivo* (see Section 2). Provisionally, the residue definition for **risk assessment** is proposed as 'dimethoate and omethoate'. For **monitoring**, the residue definition is proposed as 'dimethoate and omethoate, to be considered separately'.

Sufficient residue trials compliant respectively with the northern Europe (NEU) and southern Europe (SEU) outdoor GAPs on wheat (extrapolation to rye and triticale) have been submitted and determined the magnitude of dimethoate and omethoate residues in grain and straw. A data gap was, however, set to demonstrate that the maximum storage time period of the straw samples in the field trials on wheat is covered by valid storage stability data for dimethoate and omethoate in order to validate these residue trials (data gap). Seven and three residue trials compliant, respectively, with the NEU and SEU GAPs on sugar beet (with a possible extrapolation to turnips and beetroots) were submitted for the determination of dimethoate residues. Since all residue levels were below the LOQ, only one additional residue trial on sugar beet roots and tops and leaves and compliant with the SEU GAP is required to complete the residue data set (data gap). As for omethoate residues were demonstrated to be stable within 1 month only in sugar beet root under frozen storage conditions, sufficient residue trials on sugar beet compliant, respectively, with the NEU and SEU GAPs and analysing for omethoate residues in the roots within 1 month after sampling are required (data gap). Residues of metabolites **III, XX, XII, X, XI** and **XXIII** were also analysed in wheat grain and straw and in sugar beet root and tops/leaves but for most of these metabolites, the storage conditions used for the samples in the wheat and sugar beet residue trials were not covered by valid storage stability data.

Currently, based on the agreed provisional plant residue definition for risk assessment, the livestock dietary burden calculation has been performed separately for dimethoate and omethoate and should be revised pending finalisation of the residue definition in plants (see also Section 2) and the assessment of the requested outstanding data (see data gaps in Section 7).

Poultry and ruminant metabolism studies conducted with $^{14}$C-methoxy-labelled dimethoate showed a similar metabolic pattern in all matrices. Dimethoate was extensively metabolised in all animal matrices

and was never detected in any matrix whilst omethoate was identified in hen and goat liver (10% TRR; 0.081–0.120 mg eq/kg) and in egg white (3% TRR; 0.004 mg eq/kg) only; the metabolite **III** accounted for up to 16% TRR (0.131 mg eq/kg) in liver, 4% TRR (0.005 mg eq/kg) in egg white and 8% TRR (0.019 mg eq/kg) in milk. The major part of the radioactive residues was shown to be incorporated into phosphorylated natural compounds (57% TRR in hen fat to 100% TRR in hen muscle).

Poultry and ruminant feeding studies were conducted with dimethoate only and the magnitude of dimethoate and omethoate residues was determined in all matrices. At all the dosing levels, dimethoate and omethoate residues were below the LOQ of 0.001 mg/kg in the poultry tissues and eggs. From the ruminant feeding study, quantifiable residues of dimethoate were recovered in fat only at all dosing levels (0.0014–0.0268 mg eq/kg); residues of dimethoate in all other matrices were below the LOQ of 0.001 mg/kg. Residues of omethoate occurred at the highest dimethoate dosing level (ca. 135 N) in milk (max. 0.0187 mg eq/kg), liver (0.0054 mg eq/kg), kidney (0.0047 mg eq/kg), muscle (0.0049 mg eq/kg) and in fat (0.004 mg eq/kg). Uncertainties still remain on the actual residue levels of omethoate in kidney as integrity of the residues during sample storage prior to analysis was not demonstrated for this compound.

Based on these observations, the peer review agreed to set the residue definition for **risk assessment** for livestock as 'dimethoate and omethoate'. For **monitoring**, the definition is proposed as 'dimethoate and omethoate, to be considered separately'. These residue definitions should be considered as provisional as a mutagenic potential could not be ruled out for dimethoate, and omethoate is concluded to be mutagenic *in vivo* (see Section 2).

Since the transfer of total dimethoate and omethoate residues in animal matrices has to be addressed, ruminant and poultry feeding studies conducted with omethoate or with simultaneous administration of dimethoate and omethoate at a ratio representative of the ratio of both substances in feed items need to be provided analysing dimethoate and omethoate residues in all animal matrices (data gap). According to the current legislation on animal health and considering that a mutagenic potential could not be ruled out for dimethoate, and furthermore omethoate is concluded to be mutagenic *in vivo*, further consideration should be given to the impact on animal health following the transfer of residues of dimethoate and omethoate present in feed items and the *in vivo'* formation of omethoate residues in animal matrices when the animals are fed with dimethoate.

As sugar beet is not a feed item and residues of dimethoate and omethoate are not expected to exceed 0.01 mg/kg in wheat grain, a fish metabolism study is not triggered

According to the representative uses, wheat can be treated at the flowering stage and it cannot be excluded that sugar beet may be harvested after flowering for seed production. These crops can therefore be visited for pollen and/or nectar collection. Deficiencies were identified in the semifield trials on *Phacelia* as the residues of dimethoate and omethoate were determined in pollen only and not in nectar which is relevant for the representative use on sugar beet; furthermore, there was evidence of cross contamination of the control samples. Therefore, the available information is considered insufficient to rule out potential residues of dimethoate and omethoate in pollen and bee products for human consumption (data gap).

Since a mutagenic potential could not be excluded for dimethoate, toxicological reference values could not be established and a dietary risk assessment for the consumers could not be conducted. Furthermore, since omethoate was concluded to be an *in vivo* mutagen, the setting of toxicological reference values for this metabolite is not considered appropriate. This leads to a critical area of concern (see also Section 2).

The consumer risk assessment from the consumption of drinking water is also not finalised considering the lack of appropriate information to address the effect of water treatment processes on the nature of residues of the active substance and its identified metabolites omethoate and metabolite **X**, potentially present in surface water, when surface water is abstracted for drinking water (see Section 4).

## 4. Environmental fate and behaviour

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, dimethoate exhibited low persistence, forming the major (> 10% AR) metabolite **X** (max. 4.3% AR), which exhibited very low persistence. Mineralisation of the carbonyl $^{14}C$ radiolabel to carbon dioxide accounted for 53.3% AR after 21 days. The formation of unextractable residues (not extracted by acetonitrile/water) for this radiolabel accounted for 42.4% AR after 121 days. In anaerobic soil incubation, the degradation pathway was similar to that under aerobic conditions. In a soil photolysis

study, metabolites *O,O*-dimethyl thiophosphoric acid (Met **XVI**) and metabolite **XVII** were formed at 58.9% AR and at 27.9% AR, respectively. The contribution of photolytic transformation processes on soil surfaces to the dissipation of dimethoate from the soil environment is regarded as not relevant.

In satisfactory field dissipation studies carried out at four sites in Europe (Germany, the Netherlands, Spain and Italy) and one site in the US (spray application to the soil surface on bare soil plots in summer) dimethoate exhibited low persistence, forming the major (> 10% AR) metabolite omethoate (max. 15.4% AR), which exhibited very low to moderate persistence. Field study time for 50% of a substance to degrade (DegT50) values were derived following normalisation to FOCUS reference conditions (20°C and PF2 soil moisture) following the EFSA (2014a) DegT50 guidance. The field data endpoints were combined with lab values to derive modelling endpoints for both dimethoate and the metabolite omethoate.

Dimethoate exhibited very high to high mobility in soil. It was concluded that the adsorption of dimethoate was not pH dependent. Reliable mobility data could not be generated for the metabolites omethoate, metabolite **X**, **XVI** and **XVII,** due to their rapid degradation, therefore $K_{Foc}$ were determined using QSPR method (using EPISuite v. 4.11).

In laboratory incubations in dark aerobic natural sediment water systems, dimethoate exhibited moderate persistence, forming the major metabolite **X** (max. 17% AR in water and only 5% max. in sediment). The unextractable sediment fraction (not extracted by acetonitrile/water) for the carboxy $^{14}C$ radiolabel accounted for 40–51% AR at study end (105 days). Mineralisation of this radiolabel accounted for 24–28% AR at the end of the study. The rate of decline of dimethoate in a laboratory sterile aqueous photolysis experiment was slow relative to that occurred in the aerobic sediment water incubations. No chromatographically resolved component (excluding dimethoate) accounted for > 10% AR. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites **X, XVI** and **XVII**, using the FOCUS (2001) step 1 and step 2 approach (version 3.2 of the Steps 1-2 in FOCUS calculator). For the active substance dimethoate and metabolite omethoate, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available.[6] The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 91–93% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% and erosion runoff of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers may wish to note that whilst run-off mitigation is included in the step 4 calculations available, the FOCUS (2007) report acknowledges that for substances with $K_{Foc}$ < 2,000 mL/g (i.e. dimethoate), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4[6] for the active substance dimethoate and metabolites omethoate, **X, XVI** and **XVII**. The potential for groundwater exposure from the representative uses by dimethoate above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios for dimethoate and these metabolites.

PECs were calculated using a risk envelope approach to cover all proposed uses: sugar beets – 200 g a.s./ha covering lower application rate and winter cereals – 200 g a.s./ha covering summer application.

The applicant only provided information to address the effect of water chlorination on the residues of dimethoate and omethoate. Therefore, appropriate information to address the effect of water treatment processes on the nature of residues of the active substance and its identified metabolites omethoate and metabolite **X**, potentially present in surface water, when surface water is abstracted for drinking water, was not provided in order to assess the consumer risk from the consumption of drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

[6] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

# 5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013b).

It is noted that for some studies included in the original draft assessment report, only short summaries were available not allowing for a proper re-evaluation (data gap).

The available data were not sufficient to support the compliance of the technical specification with the batches used in the ecotoxicological studies (data gap and critical area of concern).

Several aspects of the risk assessment for dimethoate were discussed at the Peer Review Experts' meeting 177 in April 2018.

In some cases, a different formulation than the representative one was used in the ecotoxicological toxicity tests. However, based on all the available information, bridging between the formulations was supported.

Based on the available data and Tier I acute risk assessment, low risk to **birds** was identified for the representative use on wheat and sugar beet at the lowest application rate while high risk to small granivorous and small insectivorous birds was identified for the representative use on sugar beet (200 g/ha). With a refinement based on an appropriate crop interception factor, a low acute risk was identified for small granivorous birds.

Several refinements were available, such as selection of focal species, proportion of different food types (PD) and effect field studies.[7] Two focal species were proposed on the basis of studies conducted in sugar beet fields in Greece and Germany: the skylark (*Alauda arvensis*), as a small omnivorous species for northern and central Europe and yellow wagtail (*Motacilla flava*), as a small insectivorous species for both northern, central and southern Europe. These focal species were already accepted for the confirmatory data assessment (EFSA, 2013a) and were reconfirmed. Refined diet composition for skylark based on literature data was considered acceptable. The use of a variable diet for skylark based on data from northern EU was in principle also agreed. However, since no information was provided for extrapolating the diet composition to central EU, further consideration at national level is recommended. For the yellow wagtail, the available information in support of the diet composition was not considered sufficient. One reliable field effect study on sugar beet was available. In this study, only one bird out of the radiotracked individuals was found dead. This, however, might also be due to the difficulties in finding carcasses in field. In addition, six chicks were found dead immediately after spraying and the experts agreed that it cannot be excluded that the mortality was treatment related. Based on the overall available information, high acute risk to birds was concluded for the representative use on sugar beet.

Even after re-evaluation and comparison with historical control data, a valid chronic endpoint could not be established from the available study with bobwhite quail since effects were also observed at the lowest tested concentration. A benchmark dose (BMD) analysis was also available;[8] however, its use was not considered suitable as too many uncertainties were identified, also linked to the lack of a clear guidance on the use of such kind of analysis for avian toxicity studies (data gap). The available field studies in wheat and sugar beet presented several limitations and therefore were not considered suitable to conclude low risk to birds (data gap). Due to the lack of a valid chronic endpoint, the risk assessment for birds could not be finalised for all the relevant routes of exposure.

Based on the available and agreed endpoints, low acute risk to **mammals** was identified while high chronic risk was identified for the majority of the relevant Tier 1 scenarios for all the representative uses.

Refinements taking into account the residue decline in the relevant crops, in arthropods and in ground vegetation and a field effect study in sugar beet were available.[9] The available data were not considered suitable to support the use of a refined residue decline in both wheat and sugar beet since for the majority of the trials the sampling interval was not appropriate and not done following the recommendation of the EFSA Guidance (EFSA, 2009), the application of the test item was done at later growth stages than specified for the representative use, etc. For the residue decline in arthropods and ground vegetation, only one study conducted in Germany was available and thus not considered sufficient for the use of a refined $DT_{50}$ value.

[7] Refer to experts' consultation 5.3 in the Report of Pesticides Peer Review Experts' Meeting 177.
[8] Refer to experts' consultation 5.1 in the Report of Pesticides Peer Review Experts' Meeting 177.
[9] Refer to experts' consultation 5.2 in the Report of Pesticides Peer Review Experts' Meeting 177.

Information was available to support the irrelevance of the small herbivorous mammals' scenario for the representative uses. This, however, was not confirmed by the available field effect study demonstrating that common voles can occur in sugar beet fields. In addition to the above argumentation, no other focal species was proposed for further addressing the risk to small herbivorous mammals and therefore a high risk was concluded (data gap and critical area of concern).

The available information on the selection of a specific focal species for small omnivorous mammals and large herbivorous mammals was not deemed as sufficient.

No effect field studies were available on wheat. It was proposed to extrapolate from sugar beet to wheat. The available field effect study on sugar beet presented deficiencies such as low number of plots all located in Germany, lack of a statistical analysis, etc., hence, it was not considered sufficient to conclude a low risk to mammals for the representative uses on sugar beet and wheat (data gap and critical area of concern).

Higher tier studies were not available for the use on sugar beet at the application rate of 120 g a.s./ha. Therefore, in the absence of specific data and considering the overall evidence, the same conclusion is drawn for both the representative uses on sugar beet (at 120 g a.s./ha and 200 g a.s./ha).

The pertinent metabolite omethoate showed to be more toxic to birds and mammals than dimethoate. No chronic data on birds were, however, available (data gap and issue not finalised). An approach for the combined risk assessment between dimethoate and omethoate was presented. However, since the combined risk assessment was performed assuming that dimethoate is totally converted to omethoate, the outcome is considered overly conservative. When conducting a separate risk assessment for omethoate and using the agreed refinement (crop interception), a high acute risk to birds for the representative uses on sugar beet and to mammals for the representative use on wheat and sugar beet at 200 g a.s./ha and high chronic risk for all the representative uses was identified for mammals (data gap and critical area of concern).

A low risk via secondary poisoning and exposure to contaminated water was concluded for mammals for both dimethoate and omethoate.

A risk assessment considering other pertinent plant metabolites **XXIII** and **XII** was not conducted (issue not finalised).

Toxicity data were available on all the relevant **aquatic** taxa for dimethoate and the pertinent metabolite omethoate. Regarding the representative formulation, acute data for fish and invertebrates were available as well as data on algae. No exposure estimates were available for the representative use on sugar beet at the application rate of 120 g a.s./ha (data gap). Based on those data, low risk was concluded on fish (acute and chronic), aquatic invertebrates (acute) and algae by using Step 1 & Step 2 FOCUS $PEC_{sw}$. A low chronic risk to aquatic invertebrates was concluded for all the relevant FOCUS scenarios except for the D2 for the representative use on wheat (data gap). For the representative use on sugar beet, low risk to aquatic invertebrates was concluded by using Step 3 FOCUS $PEC_{sw}$ for all the relevant scenarios except for the R3 for which mitigation measures up to 10 m buffer zone and 10 m vegetative filter strip were needed.

For omethoate, a low risk for fish and algae was concluded while high acute risk for aquatic invertebrates was identified. Since data on seven additional species were available, a refinement based on the species sensitivity distribution was possible, which allowed to conclude a low risk for all the representative uses. A low chronic risk for aquatic invertebrates was concluded for all the relevant scenario except D2 for the representative use on wheat (data gap). For the scenarios R1 and R3 for the representative use on sugar beet, mitigation measures up to 20 m buffer zone and 20 m vegetative filter strip were needed to conclude low risk to invertebrates.

Considering that the pertinent metabolite omethoate is an insecticide and exhibited a higher toxicity than dimethoate, a combined risk assessment[10] was also presented for aquatic invertebrates being the most sensitive organisms. Based on this assessment, low acute and chronic risk was concluded for all the scenarios except for situation represented by the D2 scenario (FOCUS Step 3 $PEC_{sw}$) for the representative use on wheat. For the representative use on sugar beet (200 g a.s./ha), low risk was concluded for all the relevant FOCUS scenarios except for R3. In addition, for concluding low risk on aquatic invertebrates for the scenario R1, mitigation measures up to 20 m buffer zone and 20 m vegetative filter strip need to be implemented.

For the other pertinent aquatic metabolites (Met X, XVI and XVII), low risk was concluded by using FOCUS step 1 $PEC_{sw}$.

[10] Refer to experts' consultation 5.4 in the Report of Pesticides Peer Review Experts' Meeting 177.

Acute (contact and oral) data on **honeybees** were available as well as acute (contact and oral) toxicity data on bumblebees. No reliable data were available for honeybee larvae and adult chronic (data gap). A high risk to adult honeybees was concluded based on EFSA (2013b) for all the representative uses. The same conclusion on the acute risk assessment is drawn by using the SANCO Guidance on Terrestrial ecotoxicology (2002).

A number of (semi)field studies was available to refine the risk to honeybees.[11] For the treated crop scenario on wheat, a high risk was concluded considering that lethal and sublethal effects were observed several days after application even when the substance was applied after bee flight. The same conclusion is drawn for the representative uses on sugar beet when it is not harvested before flowering. When sugar beet is harvested before flowering, low risk to honeybees is concluded. A high risk to honeybees cannot be excluded when flowering weeds are present in the field. Considering the overall information, an exclusion period (avoiding exposure of honeybees) from the treated field of 10 days was proposed as mitigation measure. However, this was not considered as sufficiently supported by data.

A semifield study was available to investigate effects of dimethoate on bees at off-field drift rate. Although no effects on foragers were observed, this type of study does not allow drawing a conclusion on colony strength, including brood and therefore low risk to honeybees could not be demonstrated for off-field situations. It is considered that the available studies covered both dimethoate and omethoate as the latter was detected when residues analysis was performed. Therefore, high risk was also concluded for the pertinent metabolite (data gap and critical area of concern). Given the fast degradation of dimethoate in soil, low risk for succeeding crops was concluded.

A high acute risk to bumblebees was identified by using EFSA (2013b). The available higher tier data did not cover bumblebees (data gap).

A suitable assessment for accumulative effects was not available. A risk assessment considering exposure to contaminated water was not presented (data gap). No information was available on solitary bees.

By using the available data and Tier I risk assessment, high risk on **non-target arthropods** was identified. Extended/aged residue studies were only available on two species. Based on those data, a high risk (off-field) was identified. Field studies testing off-field rate were available.[12] The studies were, however, not conducted in an off-field habitat. Therefore, if on one hand they were not considered suitable to refine the off-field risk, on the other hand the results of those studies did not confirm the outcome of the Tier II in-field risk assessment as they showed long-lasting effects on some taxa even at lower application rate than the representative uses (data gap and critical area of concern).

Low risk to **earthworms**, **soil macroorganisms other than earthworms** and **soil microorganisms** was concluded using laboratory studies. A field study investigating effects on Collembola and Acari was also available. The study showed effects on the investigated taxa; however, recovery occurred within one year.

Low risk to **non-target terrestrial plants** and **organisms involved in biological methods for sewage treatment** was concluded.

To address the potential for endocrine disruption of dimethoate, in the ecotoxicology area, a fish short-term reproduction assay (FSTRA) and an amphibian metamorphosis assay (AMA) were available. The study on fish showed effects on fecundity (number of eggs per female) and on the gonadosomatic index in males at the highest tested concentration. However, the effects in males were observed in conjunction with effects on body weight. In the available AMA, effects in thyroid histopathology (thyroid gland hypertrophy and changes in follicular cell height) were recorded. Based on the above and pending on the data gap identified in Section 2, further ecotoxicological assessment may be needed to further elucidate the endocrine-disrupting properties of dimethoate in non-target organisms other than mammals.

[11] Refer to experts' consultation 5.5 in the Report of Pesticides Peer Review Experts' Meeting 177.
[12] Refer to experts' consultation 5.6 in the Report of Pesticides Peer Review Experts' Meeting 177.

# 6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

**Table 1:** Soil

| Compound (name and/or code) | Persistence | Ecotoxicology |
|---|---|---|
| **Dimethoate** | Low persistence<br>Single first-order $DT_{50}$ 2.3–4.3 days ($DT_{90}$ 7.8–14.1 days; laboratory conditions at 20°C, 40% MWHC soil moisture)<br>EU and US field dissipation studies single first-order $DT_{50}$ 1.9–5.0 days | Low risk to soil organisms |
| **Omethoate** (Met II) | Very low persistence<br>Single first-order $DT_{50}$ 0.1–0.4 days ($DT_{90}$ 0.2–1.2 days; laboratory conditions at 20°C, 40% MWHC soil moisture)<br>Very low to moderate persistence<br>EU and US field dissipation studies single first-order $DT_{50}$ 0.3–10.6 days | Low risk to soil organisms |
| ***O*-Desmethyl dimethoate** (Met X) | Very low persistence<br>Single first-order $DT_{50}$ 0.3–0.6 days ($DT_{90}$ 1.0–2.0 days; laboratory conditions at 20°C, 40% MWHC soil moisture) | Low risk to soil organisms |
| ***O,O*-Dimethyl thiophosphoric acid** (Met XVI) | Very low persistence<br>Single first-order $DT_{50}$ 0.3–0.4 days ($DT_{90}$ 1.0–1.4 days; laboratory conditions at 20°C, 40% MWHC soil moisture) | Low risk to soil organisms |
| ***O,O*-Dimethyl phosphoric acid** (Met XVII) | Very low persistence<br>Single first-order $DT_{50}$ 0.3–1.4 days ($DT_{90}$ 1.0–4.7 days; laboratory conditions at 20°C, 40% MWHC soil moisture) | Low risk to soil organisms |

$DT_{50}$: period required for 50% dissipation; $DT_{90}$: period required for 90% dissipation; MWHC: maximum water-holding capacity.

**Table 2:** Groundwater

| Compound (name and/or code) | Mobility in soil | > 0.1 µg/L at 1 m depth for the representative uses[a] | Pesticidal activity | Toxicological relevance |
|---|---|---|---|---|
| **Dimethoate** | Very high to high mobility<br>$K_{Foc}$ 16–52 mL/g | No | | Yes |
| **Omethoate** (Met II) | Very high mobility<br>$K_{Foc}$ 10 mL/g<br>(estimated by QSPR method) | No | | Yes<br>Rat oral $LD_{50}$ = 22 mg/kg bw Acute Tox. 2 'Fatal if swallowed'<br>*In vivo* mutagen |
| ***O*-Desmethyl dimethoate** (Met X) | Very high mobility<br>$K_{Foc}$ 10 mL/g<br>(estimated by QSPR method) | No | | No<br>Rat oral $LD_{50}$ = 337 mg/kg bw (Acute Tox. 4 'Harmful if swallowed')<br>No genotoxic potential<br>Does not share the developmental toxicity observed with the parent |
| ***O,O*-Dimethyl thiophosphoric acid** (Met XVI) | Very high mobility<br>$K_{Foc}$ 12 mL/g<br>(estimated by QSPR method) | No | | No data, assessment not triggered |
| ***O,O*-Dimethyl phosphoric acid** (Met XVII) | Very high mobility<br>$K_{Foc}$ 5 mL/g<br>(estimated by QSPR method) | No | | No data, assessment not triggered |

$K_{Foc}$; Freundlich organic carbon adsorption coefficient; QSPR: quantitative structure–property relationship; $LD_{50}$: lethal dose, median; bw: body weight.
(a): FOCUS scenarios or a relevant lysimeter.

**Table 3:** Surface water and sediment

| Compound (name and/or code) | Ecotoxicology |
|---|---|
| **Dimethoate** | High risk for 1 out of 9 exposure scenarios for wheat and 1 out of 4 for sugar beet[a] |
| **Omethoate** (Met II) | High risk for 1 out of 9 exposure scenarios for wheat and 1 out of 4 for sugar beet[a] |
| ***O*-Desmethyl dimethoate** (Met X) | Low risk to aquatic organisms |
| ***O,O*-Dimethyl thiophosphoric acid** (Met XVI) | Low risk to aquatic organisms |
| ***O,O*-Dimethyl phosphoric acid** (Met XVII) | Low risk to aquatic organisms |

(a): For the representative use on sugar beet at 200 g a.s./ha, high risk is identified in situation represented by the FOCUS scenario R3 only in case a combined risk assessment is performed between dimethoate and omethoate. When a separate risk assessment is conducted, low risk is concluded with the implementation of mitigation measures (see Section 5).

**Table 4:** Air

| Compound(name and/or code) | Toxicology |
|---|---|
| **Dimethoate** | Rat $LC_{50}$ inhalation: 1.68 mg/L air (4 h, whole body); Acute Tox. 4, H332 'Harmful if inhaled' |
| **Omethoate** | Rat $LC_{50}$ inhalation: 0.287 mg/L air (4 h; nose only); Acute Tox. 2, H330 'Fatal if inhaled' |

$LC_{50}$: lethal concentration, median.

# 7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

## 7.1. Data gaps identified for the representative uses evaluated

- A data gap has been identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on health, the environment and non-target species and published within the 10 years before the date of submission of the dossier. Specifically, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2, 3, 4 and 5).
- An analytical method for monitoring of dimethyldithiophosphate in body fluids is missing (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1)
- An assessment of the toxicological relevance of the individual impurities present in the technical specification in comparison with the toxicological profile of the parent compound, dimethoate, is missing (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2)
- Clarification of the gene mutation potential in robust *in vivo* follow up to the positive mutagenic effects observed in bacterial and mammalian cells *in vitro* with dimethoate should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- In EFSA's view, the experts may not have had the full information available to conclude on the endocrine disruptor (ED) potential of dimethoate. The RMS revised the conclusion after the experts meeting taking into consideration the US EPA conclusion that an interaction of dimethoate with the thyroid pathway in mammals and wildlife cannot be excluded. Accordingly, this issue has to be clarified (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5)
- The composition of the formulation used in the bystander and resident exposure refinement scenario 2 – although currently a non-dietary risk assessment cannot be conducted should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Storage stability data for dimethoate and omethoate residues in cereal straw and covering the maximum storage time period of the samples from the residue trials on wheat are lacking (relevant for the representative use evaluated in wheat, rye, triticale, durum wheat; submission date proposed by the applicant: unknown; see Section 3).
- One residue trial on sugar beet, compliant with the SEU GAP for the determination of dimethoate residues in roots and tops and leaves, should be provided (relevant for the representative use in sugar beet, turnips, beetroots; submission date proposed by the applicant: unknown; see Section 3).
- Sufficient residue trials on sugar beet, compliant, respectively, with the NEU and SEU GAPs and analysing omethoate residues in the roots, within 1 month after sampling are required (relevant for the representative use in sugar beet, turnips, beetroots; submission date proposed by the applicant: unknown; see Section 3).
- Ruminant and poultry feeding studies conducted with omethoate or with simultaneous administration of dimethoate and omethoate at a ratio representative of the ratio of both substances in feed items and analysing dimethoate and omethoate residues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Data on residue levels of dimethoate and omethoate in pollen and bee products for human consumption as set out in current data requirements in Regulation (EU) No 283/2013 should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).

- The effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water (Article 4 (approval criteria for active substances) 3. (b) of Regulation (EC) No 1107/2009) has not been assessed. A consideration of the processes of ozonation may be considered appropriate. If an argumentation is made that concentrations at the point of extraction for drinking water purposes will be low, this argumentation should cover metabolites omethoate and metabolite X predicted to be in surface water, as well as the active substance (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information to support the compliance of the technical specifications and the batches used in the ecotoxicological studies should be provided (relevant for all the representative uses; submission date: unknown; see Section 5); extended study summaries for all the studies included in the original draft assessment report should be submitted (relevant for all the representative uses; submission date: unknown; see Section 5);
- Further data to address the risk to birds for dimethoate and omethoate for all the relevant routes of exposure including a valid chronic endpoint should be submitted (relevant for all the representative uses; submission date: unknown; see Section 5);
- Further data to address the risk to birds and mammals when exposed to the pertinent plant metabolites XXIII and XII (relevant for all the representative uses; submission date: unknown; see Section 5);
- Further data to address the risk to mammals for dimethoate and omethoate are missing (relevant for all the representative uses; submission date: unknown; see Section 5);
- Further data to address the risk to aquatic invertebrates for dimethoate and omethoate in situation represented by D2 FOCUS scenario and R3 FOCUS scenario[13] are missing (relevant for the representative use on wheat and sugar beet, respectively; submission date: unknown; see Section 5);
- Exposure estimates for surface water for dimethoate and omethoate are missing (relevant for the representative use on sugar beet at the application rate of 120 g a.s./ha; submission date: unknown; see Sections 4 and 5).
- Further data to address the risk to honeybees (adults and larvae) for dimethoate and omethoate, including a risk assessment for exposure through contaminated water should be provided (relevant for all the representative uses; submission date: unknown; see Section 5);
- Further data to address the risk to bumblebees should be provided (relevant for all the representative uses; submission date: unknown; see Section 5);
- Further data to address the risk (in-field and off-field) to non-target arthropods are missing (relevant for all the representative uses; submission date: unknown; see Section 5);

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

## 8.1. Particular conditions proposed for the representative uses evaluated

- Mitigation measures up to 10 m buffer zone and 10 m vegetative filter strip are needed to conclude low risk to aquatic organisms (invertebrates) for dimethoate for the scenario R3 for the representative use on sugar beet 200 g a.s./ha(see Section 5).
- Mitigation measures up to 20 m buffer zone and 20 m vegetative filter strip are needed to conclude low risk to aquatic organisms (invertebrates) for omethoate for the scenario R1 and R3[14] for the representative use on sugar beet 200 g a.s./ha (see Section 5).

[13] For the representative use on sugar beet at 200 g a.s./ha, high risk is identified in situation represented by the FOCUS scenario R3 only in case a combined risk assessment is performed between dimethoate and omethoate. When a separate risk assessment is conducted low risk is concluded with the implementation of mitigation measures (see Section 5).

[14] For the FOCUS scenario R3, low risk is concluded based on the above mitigation measures only in case a separate risk assessment is conducted for dimethoate and omethaote. When a combined risk assessment is performed, for that scenario high risk is still indicated even with the implementation of mitigation measures (see Section 5).

# 9. Concerns

## 9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[15] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

1) Dimethoate is proposed to be classified as toxic for reproduction category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, and toxic effects on the endocrine organs have been observed in the available data (effects on male reproductive organs); therefore the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine-disrupting properties may be met. From a scientific perspective, the experts may not have had the full information available to conclude on the ED potential of dimethoate. The RMS revised the conclusion after the experts meeting taking into consideration the US EPA conclusion that an interaction of dimethoate with the thyroid pathway in mammals and wildlife cannot be excluded. This issue could not be finalised (see Sections 2 and 5).
2) The chronic risk assessment for birds could not be finalised since a reliable endpoint could not be derived (see Section 5).
3) The risk assessment for birds and mammals when exposed to the relevant plant metabolites XXIII and XII could not be finalised (see Section 5).
4) The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water that might contain dimethoate and metabolites omethoate and *O*-desmethyl dimethoate (see Section 4).

## 9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

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

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

5) The technical specification (either the current or the revised one) is not supported by the (eco)toxicological assessment (see Sections 2 and 5).
6) Positive gene mutation effects were observed in bacterial and mammalian cells *in vitro* with dimethoate without appropriate *in vivo* follow-up (see Section 2).

[15] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

7) Omethoate was concluded to be an *in vivo* mutagen, no threshold for this effect is assumed and the setting of toxicological reference values for this metabolite is not considered appropriate (see Sections 2 and 3).
8) Since a mutagenic potential could not be excluded for dimethoate, no threshold for this effect is assumed and therefore toxicological reference values could not be established. Dietary and non-dietary exposure risk assessment could not be conducted (see Sections 2 and 3).
9) High risk to mammals was concluded for all the assessed representative uses (see Section 5)
10) High risk to honeybees was concluded for all the assessed representative uses for both dimethoate and omethoate (see Section 5)
11) High risk to non-target arthropods was concluded for all the assessed representative uses (see Section 5).

## 9.3. Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

The technical material specification proposed was not comparable to the material used in the testing that would be used to derive the toxicological reference values.

**Table 5:** Overview of concerns

| Representative use | | Sugar beet (0.20 kg a.s./ha) | Sugar beet (0.12 kg a.s./ha) | Wheat |
|---|---|---|---|---|
| **Operator risk** | Risk identified | X[6,7] | X[6,7] | X[6,7] |
| | Assessment not finalised | | | |
| **Worker risk** | Risk identified | X[6,7] | X[6,7] | X[6,7] |
| | Assessment not finalised | | | |
| **Resident/bystander risk** | Risk identified | X[6,7] | X[6,7] | X[6,7] |
| | Assessment not finalised | | | |
| **Consumer risk** | Risk identified | X[6,7,8] | X[6,7,8] | X[6,7,8] |
| | Assessment not finalised | X[4] | X[4] | X[4] |
| **Risk to wild non-target terrestrial vertebrates** | Risk identified | X[8] | X[8] | X[8] |
| | Assessment not finalised | X[2,3] | X[2,3] | X[2,3] |
| **Risk to wild non-target terrestrial organisms other than vertebrates** | Risk identified | X[10,11] | X[10,11] | X[10,11] |
| | Assessment not finalised | | | |
| **Risk to aquatic organisms** | Risk identified | X (1 out of 4)* | | X (1 out of 9) |
| | Assessment not finalised | | | |
| **Groundwater exposure to active substance** | Legal parametric value breached | | | |
| | Assessment not finalised | | | |

| Representative use | | Sugar beet (0.20 kg a.s./ha) | Sugar beet (0.12 kg a.s./ha) | Wheat |
|---|---|---|---|---|
| **Groundwater exposure to metabolites** | Legal parametric value breached[(a)] | | | |
| | Parametric value of 10 μg/L[(b)] breached | | | |
| | Assessment not finalised | | | |

a.s.: active substance.
The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.
*: For the FOCUS scenario R3, low risk is concluded based on the use of specific mitigation measures and only in case a separate risk assessment is conducted for dimethoate and omethoate. When a combined risk assessment is performed, high risk is still indicated even with the implementation of mitigation measures for FOCUS scenario R3 (see Section 5).
(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.
(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

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## Abbreviations

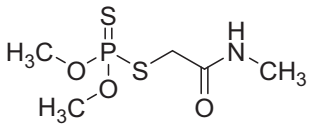
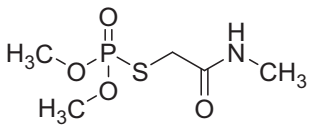
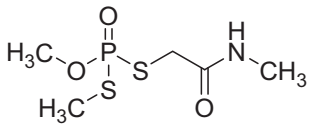
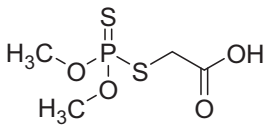
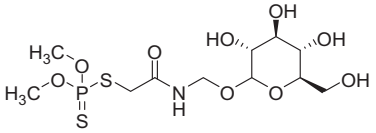
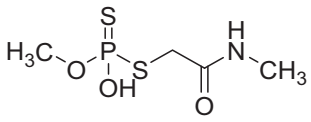
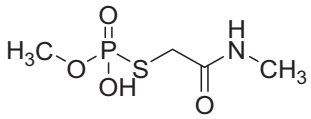
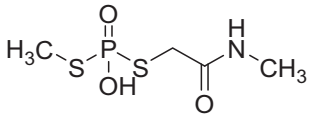
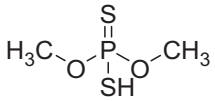
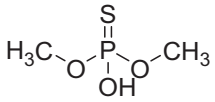
| | |
|---|---|
| a.s. | active substance |
| AAOEL | acute acceptable operator exposure level |
| AChE | Acetylcholinesterase |
| ADI | acceptable daily intake |
| AMA | amphibian metamorphosis assay |
| AOEL | acceptable operator exposure level |
| AR | applied radioactivity |
| ARfD | acute reference dose |
| BMD | benchmark dose |

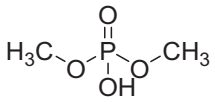
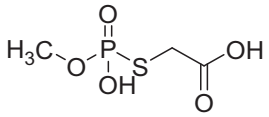
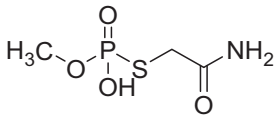
| | |
|---|---|
| bw | body weight |
| CA | chromosome aberration |
| CLP | classification, labelling and packaging |
| DAR | draft assessment report |
| DAT | days after treatment |
| DegT50 | time for 50% of a substance to degrade |
| DNT | developmental neurotoxicity |
| $DT_{50}$ | period required for 50% dissipation (define method of estimation) |
| $DT_{90}$ | period required for 90% dissipation (define method of estimation) |
| EC | emulsifiable concentrate also used for European Commission |
| ECHA | European Chemicals Agency |
| ED | endocrine disruptor |
| EEC | European Economic Community |
| FAO | Food and Agriculture Organization of the United Nations |
| FOCUS | Forum for the Co-ordination of Pesticide Fate Models and their Use |
| FSTRA | fish short-term reproduction assay |
| GAP | Good Agricultural Practice |
| GC-FPD | gas chromatography with flame photometric detector |
| GC-MS | gas chromatography – mass spectrometry |
| HPLC–MS/MS | high performance liquid chromatography with tandem mass spectrometry |
| InChiKey | International Chemical Identifier Keys |
| ISO | International Organization for Standardization |
| IUPAC | International Union of Pure and Applied Chemistry |
| JMPR | Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues) |
| $K_{Foc}$ | Freundlich organic carbon adsorption coefficient |
| $LC_{50}$ | lethal concentration, median |
| $LD_{50}$ | lethal dose, median; dosis letalis media |
| LOQ | limit of quantification |
| M/L | mixing and loading |
| MRL | maximum residue level |
| MWHC | maximum water-holding capacity |
| NEU | northern Europe |
| NOAEL | no observed adverse effect level |
| OECD | Organisation for Economic Co-operation and Development |
| PD | proportion of different food types |
| PEC | predicted environmental concentration |
| $PEC_{air}$ | predicted environmental concentration in air |
| $PEC_{gw}$ | predicted environmental concentration in groundwater |
| $PEC_{sed}$ | predicted environmental concentration in sediment |
| $PEC_{soil}$ | predicted environmental concentration in soil |
| $PEC_{sw}$ | predicted environmental concentration in surface water |
| PoD | point of departure |
| QSPR | quantitative structure–property relationship |
| QuEChERS | quick, easy, cheap, effective and safe method |
| RAR | renewal assessment report |
| RBC | red blood cells |
| SEU | southern Europe |
| SMILES | simplified molecular-input line-entry system |
| SWAN | Surface Water Assessment eNabler |
| ToxCAST | (US EPA) Toxicity Forecaster |
| TRR | total radioactive residue |
| UF | uncertainty factor |
| WHO | World Health Organization |

# Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5454

## Appendix B – Used compound codes

| Code/trivial name[a] | IUPAC name/SMILES notation/ InChiKey[b] | Structural formula[c] |
|---|---|---|
| **Dimethoate** | *O*,*O*-dimethyl *S*-methylcarbamoylmethyl phosphorodithioate<br>or<br>2-dimethoxyphosphinothioylthio-*N*-methylacetamide<br>COP(=S)(OC)SCC(=O)NC<br>MCWXGJITAZMZEV-UHFFFAOYSA-N |  |
| **Omethoate** | *O*,*O*-dimethyl *S*-methylcarbamoylmethyl phosphorothioate<br>or<br>2-dimethoxyphosphinoylthio-*N*-methylacetamide<br>COP(=O)(OC)SCC(=O)NC<br>PZXOQEXFMJCDPG-UHFFFAOYSA-N |  |
| **Isodimethoate** | *O*,*S*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] phosphorodithioate<br>or<br>*O*,*S*-dimethyl *S*-methylcarbamoylmethyl phosphorodithioate<br>COP(=O)(SC)SCC(=O)NC<br>IRZFDJFTOCCEPS-UHFFFAOYSA-N |  |
| **Metabolite III**<br>*Dimethoate carboxylic acid* | [(dimethoxyphosphorothioyl)sulfanyl] acetic acid<br>COP(=S)(OC)SCC(O)=O<br>OGCAJUKWNJKZFV-UHFFFAOYSA-N |  |
| **Metabolite V-conjugates**<br>*Hydroxy dimethoate-glucose conjugate* | *S*-(2-{[(D-glucopyranosyloxy)methyl] amino}-2-oxoethyl) *O*,*O*-dimethyl phosphorodithioate<br>COP(OC)(SCC(NCOC1O[C@@H]([C@H]([C@@H]([C@H]1O)O)O)CO)=O)=S<br>YLJBEFASBZZHBI-YKVPTUPCSA-N |  |
| **Metabolite X**<br>*O-Desmethyl dimethoate* | *O*-methyl *S*-[2-(methylamino)-2-oxoethyl] hydrogen phosphorodithioate<br>CNC(CSP(O)(OC)=S)=O<br>XEXKOGVVDDWSQB-UHFFFAOYSA-N |  |
| **Metabolite XI**<br>*O-Desmethyl omethoate* | *O*-methyl *S*-[2-(methylamino)-2-oxoethyl] hydrogen phosphorothioate<br>CNC(CSP(O)(OC)=O)=O<br>YNTUWNGYNBVEFS-UHFFFAOYSA-N |  |
| **Metabolite XII**<br>*O-Desmethyl isodimethoate* | *S*-methyl *S*-[2-(methylamino)-2-oxoethyl] hydrogen phosphorodithioate<br>CNC(CSP(O)(SC)=O)=O<br>JGBLQXVESBTRFP-UHFFFAOYSA-N |  |
| **Metabolite XV**<br>*Dimethyldithiophosphate* | *O*,*O*-dimethyl hydrogen phosphorodithioate<br>COP(S)(OC)=S<br>CZGGKXNYNPJFAX-UHFFFAOYSA-N |  |
| **Metabolite XVI**<br>*O,O-Dimethyl thiophosphoric acid* | *O*,*O*-dimethyl hydrogen phosphorothioate<br>OP(OC)(OC)=S<br>WWJJVKAEQGGYHJ-UHFFFAOYSA-N |  |

| Code/trivial name[a] | IUPAC name/SMILES notation/ InChiKey[b] | Structural formula[c] |
|---|---|---|
| **Metabolite XVII**<br><br>*O,O-Dimethyl phosphoric acid* | *O,O*-Dimethyl phosphoric acid<br>O=P(OC)(O)OC<br>KKUKTXOBAWVSHC-UHFFFAOYSA-N |  |
| **Metabolite XX**<br><br>*O-Desmethyl omethoate carboxylic acid* | {[hydroxy(methoxy) phosphoryl]sulfanyl}acetic acid<br>O=C(O)CSP(OC)(O)=O<br>CGNTVHCNUANAGZ-UHFFFAOYSA-N |  |
| **Metabolite XXIII**<br><br>*O-Desmethyl N-desmethyl omethoate* | *S*-(2-amino-2-oxoethyl) *O*-methyl hydrogen phosphorothioate<br>COP(O)(SCC(N)=O)=O<br>SEHVEUCEZBISBY-UHFFFAOYSA-N |  |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Keys.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2017.2.1 ACD/Labs 2017 Release (File version N40E41, Build 96719, 6 September 2017).
(c): ChemBioDraw v.13.0.2.3021.