Reasoned opinion on the toxicological properties and maximum residue levels for propoxur

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Abstract

In accordance with Article 43 of Regulation (EC) No 396/2005, the European Commission requested EFSA to prepare a reasoned opinion on the toxicological properties and the existing maximum residue levels (MRLs) set for propoxur. EFSA was requested to assess the toxicological properties of propoxur and derive toxicological reference values, based on the toxicological assessment performed by Health Canada. EFSA was also requested to review the information provided by Member States and the UK on the metabolism of propoxur in plants and animals and on the current MRLs, as well as the limit of quantification (LOQ) that can be achieved with analytical methods used in MRL enforcement. Based on the information available to EFSA, toxicological reference values could not be derived for propoxur. No evidence was provided by Member States and UK that the existing EU MRLs need to be maintained as import tolerances. Information to support the current MRLs or alternative MRLs have not been provided by Member States and the UK. Codex MRLs are not in place. EFSA therefore recommended lowering of all existing EU MRLs for propoxur to the LOQ. According to the EU Reference Laboratories, sufficiently validated analytical methods are available to analyse for propoxur residues in all plant and animal commodities. Lacking toxicological reference values derived at EU level, a conclusion cannot be derived whether the setting of MRLs at the LOQs is sufficiently protective for the European consumers.

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Summary

In accordance with Article 43 of Regulation (EC) No 396/2005, the European Food Safety Authority (EFSA) received a request from the European Commission on 20 May 2020 to provide a reasoned opinion on the toxicological properties and maximum residue levels (MRLs) for propoxur. In particular, EFSA was requested to assess the toxicological properties of propoxur and derive toxicological reference values, based on the toxicological assessment performed by Health Canada. In addition, EFSA was also requested to review the information provided by Member States and the UK on the metabolism of propoxur in plants and animals. Based on information from the EU Reference Laboratories for Residues of Pesticides (EURLs), the achievable limit of determination/limit of quantification (LOQ) for propoxur in different matrices should be reported. EFSA was also asked to identify whether the existing MRLs for propoxur should be maintained as import tolerances, considering information available at member state level on the origin of the existing EU MRLs. If toxicological reference values could be derived, a chronic and acute risk assessment should be performed to ensure that the MRLs proposed by EFSA, where possible, or the achievable LOQs are safe for European consumers.

Propoxur was used in plant protection products in the European Union (EU) in the past but was never assessed and approved at EU level under Directive 91/414/EEC or Regulation (EC) No 1107/2009. In 2002, a non-approval decision for the active substance was taken. EU MRLs have been established under Directive 86/362/EEC, 86/363/EEC and 90/642/EEC which were then taken over in Annexes II and IIIIB of Regulation (EC) No 396/2005. MRLs greater than the LOQ are set for a number of commodities; the origin of these MRLs (e.g. MRLs reflecting previously authorised uses in an EU Member State, previous Codex MRLs in place at the time when the MRLs were established or import tolerances) is not reported in the MRL legislation.

As propoxur has not been peer reviewed in the EU, no EU agreed reference values are available. EFSA does not have access to the original experimental toxicological studies that were submitted to Member States before the entry into force of Directive 91/414/EEC. EFSA could not get access to the dossier submitted to the competent authorities responsible for pesticide regulation in Canada (Health Canada). Therefore, EFSA assessed the summary evaluation on propoxur prepared by Health Canada, in which the setting of an acceptable daily intake (ADI) of 0.0005 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.0005 mg/kg bw for propoxur was proposed. After consultation with Member States and the UK, EFSA concluded that the information described in the summary evaluation was not sufficient and complete to allow setting reference values to be used in the dietary risk assessment for propoxur or confirming those established by the Canadian authorities.

EFSA asked Member States and the UK to share information and supporting data on uses of propoxur assessed in the past at national level for setting import tolerances (e.g. information on the Good Agricultural Practices in third countries, residue trials, information on metabolism of propoxur in plant and animal products). Since no uses of propoxur were reported to EFSA, it is concluded that the existing MRLs for propoxur probably have not been established in response to import tolerance requests. Considering that propoxur is not authorised for use in plant protection products within the European Union, and that no MRLs are established by the Codex Alimentarius Commission, the existing EU MRLs should be all lowered to the LOQ.

No information was provided by Member States and the UK to elucidate the metabolic pathway of the active substance in plants and livestock. EFSA therefore reviewed the evaluations carried out by the Joint Meeting on Pesticide Residues (JMPR) in 1973 and 1983. The information on the nature of residues in plants and livestock assessed by JMPR provided some evidence that the parent compound is an appropriate marker for detecting uses of propoxur. In addition to parent propoxur, 2-hydroxyphenyl-N-methylcarbamate (free and conjugated) was identified as a major metabolite in plants. Risk managers might consider the inclusion of this metabolite in the residue definition for enforcement to enhance control of the presence of propoxur residues in monitoring programmes, acknowledging that this will pose additional burden on laboratories. Overall, the levels of detail reported in the JMPR assessment are limited and the quality of the studies does not comply with the current scientific standards. Hence, the recommendations on the appropriate residue definition are affected by uncertainties.

According to the EURLs, residues of propoxur can be analysed in products of plant and animal origin at or above the LOQ of 0.01 mg/kg.

Lacking toxicological reference values, a definitive conclusion cannot be derived on the safety of MRLs set at the LOQ. However, by inverse calculation, EFSA noted that MRLs set at the LOQ of

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0.01 mg/kg would be sufficiently protective for European consumers, if the ADI and ARfD values for propoxur are higher than 0.00124 mg/kg bw per day and 0.0015 mg/kg bw, respectively.

The recommendations are summarised in the table below.

| Code(a) | Commodity                  | Existing MRL | Proposed MRL | Conclusion/recommendation |
|---------|----------------------------|--------------|--------------|---------------------------|
| 0110030 | Lemons                     | 0.3 LOQ      |              |                           |
| 0110040 | Limes                      | 0.3 LOQ      |              |                           |
| 0110050 | Mandarins                  | 0.3 LOQ      |              |                           |
| 0154030 | Currants (black, red and white) | 0.2 LOQ  |              |                           |
| 0154040 | Gooseberries (green, red and yellow) | 0.2 LOQ  |              |                           |
| 0241000 | Flowering brassica         | 0.5 LOQ      |              |                           |
| 0242020 | Head cabbages              | 0.5 LOQ      |              |                           |
| 0270060 | Leeks                      | 1 LOQ        |              |                           |

**Enforcement residue definition:** Propoxur

According to EFSA, there is some evidence that propoxur is an appropriate marker substance for enforcing purpose, although only limited information is available.

Risk managers might consider the inclusion of the metabolite 2-hydroxy-phenyl-\(N\)-methylcarbamate (free and conjugated) in the residue definition to enhance control of the presence of propoxur residues in monitoring programmes, acknowledging that this will pose additional burden on laboratories.

EFSA did not receive any evidence that the existing EU MRLs were set as import tolerances reflecting uses in third countries. Hence, the lowering of the existing MRLs to the LOQ is recommended.

Analytical methods to enforce MRLs at the LOQ of 0.01 mg/kg are available.

If a risk management decision is taken to include 2-hydroxyphenyl-\(N\)-methyl-carbamate (free and conjugated) in the residue definition, the availability of appropriate analytical methods and the achievable LOQ should be further explored.

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See code in Annex I of Reg. (EC) No 396/2005.

| Code     | Commodity                      | Existing MRL | Proposed MRL | Conclusion/recommendation |
|----------|--------------------------------|--------------|--------------|---------------------------|
| 0600000 to 0800000 | Tea, coffee, herbal infusions, cocoa beans, carobs, hops, spices | 0.1* LOQ   |              |                           |
| 1000000  | Products of animal origin (terrestrial animals) | 0.05* LOQ  |              |                           |
| 1040000  | Honey and other apiculture products | – LOQ      |              |                           |

MRL: maximum residue level; LOQ: limit of quantification.

*: Indicates that the MRL is set at the limit of analytical quantification (LOQ).

(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.

In addition, EFSA recommends that the active substance should be assessed as regards its inclusion in the cumulative assessment group (CAG) for neurotoxicity, since propoxur acts by inhibition of acetyl cholinesterase.
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**Background**

Propoxur is an active substance previously used in the European Union (EU) in plant protection products; in 2002 a decision was taken that the substance should not be included in Annex I to Directive 91/414/EEC\(^1\) (Commission Regulation (EC) No 2076/2002\(^2\)), since no manufacturer notified a commitment to support the active substance by preparing the necessary dossier in accordance with the provisions of Directive 91/414/EEC.

The toxicological effects of propoxur have never been evaluated by the European Food Safety Authority (EFSA) and the European Union (EU) agreed reference values are not available. A toxicological assessment was performed by the experts of the Canadian competent authorities in 2014 who established an acceptable daily intake (ADI) of 0.0005 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.0005 mg/kg bw for propoxur, based on brain cholinesterase inhibition effects (PMRA, 2014).

EU maximum residue levels (MRLs) are currently set for propoxur at levels above the limit of quantification (LOQ) for several products (i.e. lemons, limes, mandarins, currants, gooseberries, flowering brassica, head cabbages and leeks). For all other commodities, MRLs are set at the LOQ of 0.05 and 0.1 mg/kg. These MRLs were included in Annexes II and IIIB to Regulation (EC) No 396/2005\(^3\) by Commission Regulation (EC) No 149/2008\(^4\). Codex MRLs for propoxur are not in place.

In the framework of the German monitoring programme, residues of propoxur were detected in beans. Germany informed the Standing Committee on Plants, Animals, Food and Feed about those findings, as well as about concerns that certain MRLs are not sufficiently protective for European consumers when using the latest EFSA Pesticide Residues Intake Model (PRIMo rev. 3) and the toxicological reference values established by Health Canada.

Since the European Commission is now reviewing the MRLs for propoxur, EFSA was mandated on 20 May 2020 to provide scientific advice. EFSA was requested to prepare a reasoned opinion on the toxicological properties and maximum residue levels for propoxur.

The mandate was included in the EFSA Register of Questions with the reference number EFSA-Q-2020-00446 and the following subject:

**Propoxur – Reasoned opinion on the toxicological properties and maximum residue levels (MRLs)**

EFSA accepted the mandate and proceeded with the assessment in accordance with Article 43 of Regulation (EC) No 396/2005 to address the terms of reference provided by the European Commission as outlined below.

**Terms of reference as provided by the European Commission**

According to Article 43 of Regulation (EC) No 396/2005, EFSA was requested:

1) to assess the toxicological properties of propoxur and derive toxicological reference values necessary for a consumer risk assessment. If original studies are not available to EFSA, it should base its assessment on the publicly available re-evaluation decision of Health Canada;

2) to consult Member States on information about the metabolism of propoxur, assess such information and derive residue definitions for risk assessment and enforcement in products of plant and animal origin. If sufficient information is not available to EFSA, it should base its further assessment on the residue definitions for risk assessment and enforcement in products of plant and animal origin comprising propoxur only;

3) to consult the EU Reference Laboratories for Residues of Pesticides on the achievable limit of determination for propoxur in different matrices;

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\(^1\) Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1-32.

\(^2\) Commission Regulation (EC) No 2076/2002 of 20 November 2002 extending the time period referred to in Article 8(2) of Council Directive 91/414/EEC and concerning the non-inclusion of certain active substances in Annex I to that Directive and the withdrawal of authorisations for plant protection products containing these substances. OJ L 319, 23.11.2002, p. 3-11.

\(^3\) Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1-16.

\(^4\) Commission Regulation (EC) No 149/2008 of 29 January 2008 amending Regulation (EC) No 396/2005 of the European Parliament and of the Council by establishing Annexes II, III and IV setting maximum residue levels for products covered by Annex I thereto. OJ L 58, 1.3.2008, p. 1-398.
4) to consult Member States on information about Good Agricultural Practices authorised in third
countries, which could support the setting of import tolerances;
5) to assess the chronic and acute risk to consumers, based on the derived toxicological
reference values;
6) to recommend MRLs, where possible, and advise risk managers on alternative options. Where
relevant, EFSA should indicate whether the achievable LODs are sufficiently protective for
consumers.

The deadline proposed by the European Commission for finalising the reasoned opinion is
20 December 2020.

Assessment

As regards the first point of the Terms of Reference, as EFSA could not get access to the dossier
submitted to the competent authorities responsible for pesticide regulation in Canada (Health Canada),
EFSA assessed the summary evaluation on propoxur prepared by Health Canada, in which the setting
of an ADI of 0.0005 mg/kg bw per day and an ARfD of 0.0005 mg/kg bw for propoxur was proposed.
EFSA asked Member States and the UK on 30 June 2020 to provide comments on the Health Canada
toxicological evaluation and reference values for propoxur (PMRA, 2014). EFSA compiled the
comments provided during the consultation in a Member States Consultation (MSC) report (EFSA,
2020). EFSA assessment is reported in Section 2.

In order to address the second and the fourth point of the Terms of Reference, EFSA asked
Member States and the UK on 30 June 2020 to provide the following information:

- Good Agricultural Practices (GAPs) detailing the use of propoxur in the non-EU countries, which
could justify maintaining import tolerances for propoxur;
- confirmation that the notified GAPs of propoxur as plant protection products (PPP) are still
authorised;
- information on the MRLs/tolerance values currently in place in the countries for which GAPs
were notified;
- residue data related to the notified GAPs, accompanied by adequate details to decide on the
validity of the studies;
- results of plant and livestock metabolism relevant for the crops under assessment sufficient to
provide information on the nature of propoxur residues;
- residue definition for enforcement and risk assessment in products of plant and animal origin
according to the EU regulatory testing requirements, derived at national level or proposed
based on the metabolism studies assessed;
- Good Laboratory Practice (GLP) status of experimental studies submitted in the framework of
this data call.

At the end of the collection period of the GAPs and the supporting data, EFSA did not received
notification of uses of propoxur and the related supporting information (Sections 3.1 and 3.2).

As regards the third point of the Terms of Reference, EFSA contacted the EU reference laboratories
(EURLs) on 12 August 2020, asking to provide information on the availability of analytical methods for
the monitoring of propoxur in commodities of plant and animal origin as well as the appropriate lowest
LOQ achievable in the different matrices, including complex matrices (Section 3.3).

In Section 4, the fifth point of the Terms of Reference is addressed. The MRL proposals (last point
of the Terms of Reference) are outlined in Section 3.4.

The consultation report on the toxicological evaluation of propoxur (EFSA, 2020) as well as the
Evaluation Report on the analytical validations and the achievable LOQ for propoxur in different
matrices (EURLs, 2020) are considered as main supporting documents to this opinion and, thus, made
publicly available as background documents.

1. Regulatory information on the active substance and its use pattern

Propoxur is the ISO common name for 2-isopropoxyphenyl methylcarbamate (IUPAC). The chemical
structure of the active substance and its main metabolites is reported in Appendix B.
Propoxur belongs to the class of N-methylcarbamates which exhibit insecticidal activity. In the past,
the substance has been widely used in agricultural and non-agricultural sectors against household
insects and for the control of ectoparasites on domestic animals.
In 2002, a decision was taken that propoxur is not included as active substance in Annex I to Directive 91/414/EEC (Commission Regulation (EC) No 2076/2002). An EFSA conclusion or an EU peer review of the pesticide risk assessment is not available for this active substance.

EU MRLs for propoxur have been established under Directive 86/362/EEC, 86/363/EEC and 90/642/EEC which were then taken over in Annexes II and IIIB of Regulation (EC) No 396/2005 (Commission Regulation (EC) No 149/2008). MRLs are above the LOQ (ranging from 0.02 to 1 mg/kg) for a number of commodities in the groups of fruits and vegetables (lemons, limes, mandarins, currants, gooseberries, flowering brassica, head cabbages, leeks); for all other commodities, MRLs are at the LOQ of 0.05 or 0.1 mg/kg. The residue definition for enforcement purposes in plant and animal products set in Regulation (EC) No 396/2005 is propoxur parent compound.

Propoxur is not authorised for use in veterinary medicines for food producing animals in the EU. In the past, propoxur was used as active substance in biocides; however, under the current legislation for biocides the active substance is not approved for uses in the EU. The European Chemicals Agency (ECHA) derived a harmonised classification and labelling according to Regulation (EC) No 1272/2008: propoxur is classified as toxic if swallowed and very toxic to aquatic life and very toxic to aquatic life with long lasting effects.

Propoxur was first evaluated by JMPR in 1973 (FAO, 1974). In 2002 a decision was taken to revoke the existing codex maximum residue limits (CXLs).

2. Mammalian toxicity of the active substance

As propoxur has not been peer reviewed in the EU, no EU agreed toxicological reference values are available.

The toxicological profile of propoxur has been assessed by the Joint Meeting on Pesticide Residues in 1973 and 1989 (FAO, 1974, 1990) and more recently by the Health Canada Pest Management Regulatory Agency in 2014 (PMRA, 2014). However original studies available to both JMPR and Health Canada are not available to EFSA. The assessment performed by EFSA under this opinion and the Member States and UK consultation have been based upon the most recent summary assessment of the Canadian evaluation (PMRA, 2014).

PMRA re-evaluated the toxicological profile of propoxur and derived an ADI and an ARfD (see Table 1). The level of details reported in the summary document was found to be very limited and impeded a detailed assessment. EFSA, Member States and the UK noted that information such as studies on absorption, distribution, metabolism and excretion (ADME), toxicological studies on metabolites and carcinogenicity studies no observed adverse effect level (NOAEL) were not reported in the document. The available information was not considered sufficient to conclude on developmental neurotoxicity and endocrine disruption properties.

The overall assessment indicated that the likely more sensitive endpoint of toxicity is brain inhibition of cholinesterase and the lowest dose affecting this endpoint was observed in pups on post-natal day (PND) 11 after single exposure, which was the reference point for setting the reference values by the Canadian Agency. The BMDL10 of 0.054 mg/kg derived from the brain inhibition of acetylcholinesterase enzyme in PND 11 rat pups with application of an uncertainty factor (UF) of 100 was used by PMRA to set both ADI and ARfD.

Data on genotoxicity were inconclusive (i.e. positive and negative results are reported by PMRA) and urinary bladder and hepatocellular neoplasms were observed in carcinogenicity studies. Hence, according to EFSA the mode of action for tumours should be clarified by excluding a non-thresholded genotoxicity mode of action.

In conclusion, due to the several deficiencies described above and the inconclusive assessment of genotoxicity, EFSA considers that reference values to be used in the dietary risk assessment cannot be set. The validity of the toxicological reference values derived by PMRA could not be confirmed.
Propoxur acts by inhibition of acetyl cholinesterase; hence, EFSA recommends that the active substance should be assessed as regards its inclusion in the cumulative assessment group (CAG) for neurotoxicity.

3. Residues in products of plant and animal origin

3.1. Use patterns in exporting countries and residue data

In order to conclude whether the existing EU MRLs for lemons, limes, mandarins, currants, gooseberries, flowering brassica, head cabbages and leeks shall be maintained as import tolerances, EFSA asked EU Member States and the UK to share information on the GAPs assessed in the past at national level for setting import tolerances in these crops. In addition, EFSA asked for information on the approval status and the MRLs set in the countries where the use was notified and supporting studies to verify the validity and appropriateness of these MRL values.

At the end of the collection of GAPs and supporting data on 5 August 2020, no uses of propoxur were notified to EFSA. EFSA concluded that there was no evidence to justify maintaining the existing MRLs for the active substance propoxur as import tolerances.

3.2. Definition of residue for enforcement and risk assessment purpose

The residue definition for enforcement is set as propoxur in Regulation (EC) No 396/2005. Member States and UK did not provide information on the metabolism of propoxur in plants and livestock to EFSA which could be used to conclude on a residue definition for monitoring purpose in product of plant and animal origin. To provide risk managers with an indication on the appropriateness of the residue definition for enforcement comprising propoxur only, EFSA screened JMPR evaluations to retrieve information on the metabolic pathway in plants and livestock. Propoxur has been evaluated several times by the JMPR before the CXLs have been revoked in 2002. The nature of residues in plants and animals was assessed by JMPR in 1973 and re-evaluated in 1983 (FAO, 1974, 1985).

Plant metabolism

According to the JMPR assessment, metabolism studies were performed with radio-labelled propoxur injected into the stems of beans and cotton plants and following foliar application on maize and beans. These studies were conducted prior to the implementation of the GLP requirements.

Following foliar treatment, a considerable proportion of residues was eliminated by volatilisation from the surface of the application. Only a small amount of applied radioactivity penetrated the plant. The compounds in the plant were shown to be primarily parent propoxur and water-soluble metabolites, still possessing a carbamate structure. 2-Hydroxyphenyl-N-methylcarbamate (metabolite A) and 2-isopropoxyphenyl-N-hydroxymethyl carbamate (metabolite B) were tentatively identified. Metabolite A was predominant, accounting for 91.3% of the water-soluble residue fraction\(^\text{10}\); metabolite B was a minor metabolite (4.9% of the water-soluble residue fraction). The same proportion between the two metabolites (30.2% and 1.5%, respectively) was observed 6 days after the injection of propoxur in the bean plant.

\(^{10}\) The absolute and relative amount of radiolabelled residues in the water-soluble fraction were not specified in the JMPR reports.

| Toxicological reference value | Canadian evaluation (PMRA) | European evaluation (EFSA) |
|------------------------------|-----------------------------|----------------------------|
| Value                        | Comments | Value                | Comments                                |
| ADI                          | 0.0005 mg/kg bw per day     | BMDL\(_{10}\) 0.054 mg/kg, UF 100 | ADI cannot be set based on inconclusive assessment of genotoxicity and DNT associated uncertainty |
| ARfD                         | 0.0005 mg/kg bw             | BMDL\(_{10}\) 0.054 mg/kg, UF 100 | ARfD cannot be set based on inconclusive assessment of genotoxicity and DNT associated uncertainty |

BMDL: benchmark dose (lower confidence limit); UF: uncertainty factors; DNT: developmental neurotoxicity; bw: body weight; ADI: acceptable daily intake; ARfD: acute reference dose.

Table 1: Evaluation of toxicological reference values (TRV) derived by Health Canada and at EU level

| Toxicological reference value | Canadian evaluation (PMRA) | European evaluation (EFSA) |
|------------------------------|-----------------------------|----------------------------|
| Value                        | Comments | Value                | Comments |
| ADI                          | 0.0005 mg/kg bw per day     | BMDL\(_{10}\) 0.054 mg/kg, UF 100 | ADI cannot be set based on inconclusive assessment of genotoxicity and DNT associated uncertainty |
| ARfD                         | 0.0005 mg/kg bw             | BMDL\(_{10}\) 0.054 mg/kg, UF 100 | ARfD cannot be set based on inconclusive assessment of genotoxicity and DNT associated uncertainty |

BMDL: benchmark dose (lower confidence limit); UF: uncertainty factors; DNT: developmental neurotoxicity; bw: body weight; ADI: acceptable daily intake; ARfD: acute reference dose.

Toxicological properties and MRLs for propoxur
Five days after foliar application of $^{14}$C-carbonyl-labelled and isopropoxy-labelled propoxur on bean and maize plants, the residue on the leaves consisted practically only of the parent compound. Metabolite A represented less than 1% of the radioactivity.

In a further experiment, where the uptake of labelled propoxur by maize roots was investigated, the parent compound represented 50% of the residue in the plant, while metabolite A accounted for 19.2% and metabolite B for the 3.5% of the residues.

**Animal metabolism**

After oral administration to mammals, propoxur was rapidly metabolised and mainly eliminated in the urine as 2-isopropoxyphenol (M2).

After feeding 7.5 mg/kg per day of propoxur for 28 days to cattle, residues in kidney and milk accounted for 0.04 and 0.001 mg/kg, respectively. Metabolite A was present in amounts greater than the parent propoxur (0.13 mg/kg and 0.003 mg/kg, respectively). If summed, in kidney residues propoxur and metabolite A represent the 0.22% of the daily administered dose to cattle. No information on the nature and further data on the magnitude of residues of propoxur in livestock is available.

In 1973, JMPR concluded that the residues in foods of plant or animal origin consisted largely of the parent compound. In plant products, metabolites A and metabolite B occurred in a ratio of about 9:1. These metabolites, however, normally represented less than 30% of the total residue determined. According to JMPR, these two metabolites were also identified in the rat.

Information on whether parent compound and its metabolites were stable during freezer storage for the intervals that samples were stored in the experimental investigations was not provided.

JMPR recommended MRLs for the following residue definition: propoxur and the main metabolites (metabolites A and B), expressed as propoxur.

Upon request of CCPR, JMPR reconsidered the residue definition in 1983 (FAO, 1985), by re-evaluating the original data submitted to the 1973 Meeting. JMPR confirmed the previous finding that the portion of the residue that penetrated into the plants was rapidly converted to water soluble metabolites, namely to metabolite A and metabolite B. The metabolites were conjugated with plant glucosides and are not extractable with organic solvents. In bean plants, the organo-soluble residue consisted of the parent compound in the amounts of 58.7% and 50.1% after three days and one day, respectively. Following the re-evaluation, JMPR recommended that the metabolites A and B can be excluded from the definition of residues (FAO, 1985). A reasoning for the decision of including/excluding the metabolites from the residue definition was however not provided in the JMPR reports (FAO, 1974, 1985).

Overall, EFSA concluded that the limited and outdated information on the nature of residues in plants (beans, maize, cotton) and magnitude in livestock (cattle) assessed by JMPR provided some evidence that the parent compound might be an appropriate marker for detecting uses of propoxur.

Metabolite A (free and conjugated) was identified as a major metabolite in plant metabolism. Risk managers might consider its possible inclusion in the residue definition for enforcement to enhance control of the presence of propoxur residues in monitoring programs. The potential enforcement advantages to be gained from the proposal to include this metabolite should be balanced with increased complexity and potentially increased resources needed for development and implementation of an analytical method capable to enforce also metabolite A in plant and animal origin commodities.

Since information on metabolism studies performed with propoxur was not provided by Member States and the UK and those available in the JMPR reports do not meet the current scientific standards and are not sufficiently described, EFSA cannot draw a firm conclusion on the appropriate residue definitions for enforcement and further risk management considerations are required.

Since the toxicological evaluation of propoxur is inconclusive and reference values could not be set (see Section 1), further consideration on the residue definition for risk assessment are not necessary.

### 3.3. Limit of quantification (LOQ)

The EURLs provided detailed information on the availability of analytical methods for the monitoring of propoxur in commodities of plant and animal origin and the LOQ that can be achieved in routine enforcement practice (EURLs, 2020). The information is summarised below.
Foods of plant origin

Residues of propoxur can be measured in food of plant origin, such as fruits (including dried fruits), vegetables, cereals and processed products with multi-residue standard methods.

The methods apply the Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) approach. A high degree of selectivity and sensitivity is provided by gas and liquid chromatography (GC and LC) coupled to two mass spectrometers in tandem (MS/MS) for detection.

The citrate buffered QuEChERS method according to European standard for the analysis of pesticide residues EN 15662 (CEN, 2018) showed satisfactory recovery figures in the experiments conducted on high water content (tomato, cucumber), high acid content (orange, lemon) and as well as on dry commodities (oat, wheat flour and rice baby food) and in raisins. In high oil content matrices (avocado, peanut butter), recoveries were satisfactory with the modified citrate buffered QuEChERS and the extended QuEChERS method for vegetable oil samples (QuOil method).

According to the EURelS, the generally accepted default LOQ of 0.01 mg/kg for enforcement in routine analysis is achievable.

The EURelS indicated that lower detection levels were successfully validated. A screening detection limit (SDL) ranging from 0.001 to 0.005 mg/kg was established for the different plant matrix groups by enforcement laboratories across the EU (see Table 2).

Food of animal origin

Residues of propoxur can be measured in food of animal origin by liquid chromatography using citrate buffer and time-of-flight (TOF) mass spectrometry detection combined with the QuEChERS approach.

Validation was carried out in muscle, milk, egg and honey samples. Recovery data were presented only for milk.

According to the EURelS, the default LOQ of 0.01 mg/kg for enforcement in routine analysis is achievable in these matrices. The LOQ can be extended to liver, kidney and fat matrices.

An SDL ranging from 0.001 to 0.0025 mg/kg was achieved to detect propoxur in the tested matrices of animal commodities (see Table 2).

Table 2: Analytical control of propoxur in matrices of plant and animal origin

| Matrix group/crop group | Analyte | LOQ (mg/kg) | SDL (mg/kg) |
|------------------------|--------|-------------|-------------|
|                        |        | Quantitative screening | Qualitative screening |
| Dry commodities (high protein/ high starch content) | Propoxur | 0.01 | 0.001 | Oat, rice baby food, wheat flour |
| Commodities with high water content | Propoxur | 0.01 | 0.002 | Tomato, cucumber |
| Commodities with high oil content | Propoxur | 0.01 | 0.005 | Avocado, peanut butter |
| Commodities with high acid content | Propoxur | 0.01 | 0.002 | Orange, lemon |
| Commodities which are difficult to analyse | Propoxur | 0.01 | 0.010 | Raisins |
| Milk, honey | Propoxur | 0.01 | 0.005 | – |
| Egg | Propoxur | 0.01 | 0.001 | – |
| Meat | Propoxur | 0.01 | 0.0025 | – |
| Kidney/liver/fat | Propoxur | 0.01 | – | Expert judgment based on the performance of the method in other matrices |

LOQ: limit of quantification; SDL: screening detection limit.

Based on the information provided by the EURelS, EFSA concluded that propoxur can be monitored in products of plant and animal origin at or above the LOQ of 0.01 mg/kg. The quantitative validation performed meets the criteria for trueness and precision set in the guidance document SANCO/825/00 (European Commission, 2010).

For screening purposes, it is possible to reliably detect the presence of propoxur at lower levels.
3.4. MRL proposals

The existing MRLs for propoxur have been set by Regulation (EC) No 149/2008. Information to support the current MRLs or to derive alternative MRLs have not been provided by Member States and the UK. CXLs are not any longer in place.

EFSA recommends the lowering of the MRLs of 0.3 mg/kg in lemons, mandarins and limes, 0.2 mg/kg in currants and gooseberries, 0.5 mg/kg in flowering brassica and cabbages and 1 mg/kg in leeks to the limit of quantification (LOQ).

According to the EURs, residues of propoxur can be controlled in products of plant and animal origin at or above the LOQ of 0.01 mg/kg.

4. Consumer risk assessment

EFSA was asked to provide information whether the achievable LOQs are sufficiently protective for consumers. EFSA calculated the theoretical exposure (long-term and short-term exposure) using PRIMo rev. 3.1, assuming all food products covered by Annex I of Regulation (EC) No 396/2008 contain residues at a level equal to the LOQ of 0.01 mg/kg proposed by the EURs. The highest short-term exposure was calculated for potatoes and melons accounting for 1.5 µg/kg bw. Among the diets included in the PRIMo tool, the highest long-term exposure was calculated for the Dutch toddlers (1.24 µg/kg bw).

For further details on the exposure calculations, a screenshot of the Report sheets of the PRIMo for propoxur is presented in Appendix A.

Lacking toxicological reference values (see Section 2), a definitive conclusion cannot be derived on the safety of MRLs set at the LOQ. However, by inverse calculation, EFSA noted that MRLs set at the LOQ of 0.01 mg/kg as proposed by EURs would be sufficiently protective for European consumers, if the ADI and ARfD values for propoxur are higher than 0.00124 mg/kg bw per day and 0.0015 mg/kg bw, respectively.

5. Conclusions and Recommendations

In accordance with Article 43 of Regulation (EC) No 396/2005, EFSA received a mandate from the European Commission to review the MRLs for propoxur. EFSA was requested to prepare a reasoned opinion on the toxicological properties and MRLs set for propoxur, noting that propoxur was used in plant protection products in the European Union in the past but was never assessed and approved at EU level.

Based on the information available to EFSA, toxicological reference values could not be derived for propoxur. No evidence was provided that the existing EU MRLs need to be maintained as import tolerances. Information to support the current MRLs or alternative MRLs have not been provided by Member States and the UK. Codex MRLs are not any longer in place.

EFSA recommended lowering of all existing EU MRLs for propoxur to the limit of quantification (LOQ). According to the EURs, sufficiently validated analytical methods are available to analyse for propoxur residues in all plant and animal commodities. Lacking toxicological reference values derived at EU level, a conclusion cannot be derived whether the setting of MRLs at the LOQs is sufficiently protective for the European consumers.

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Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| ADI          | acceptable daily intake |
| ADME         | absorption, distribution, metabolism and excretion |
| ARfD         | acute reference dose |
| BBCH         | growth stages of mono- and dicotyledonous plants |
| bw           | body weight |
| CAG          | cumulative assessment group |
| CCPR         | Codex Committee on Pesticide Residues |
| CEN          | European Committee for Standardization (Comité Européen de Normalisation) |
| CXL          | codex maximum residue limit |
| ECHA         | European Chemicals Agency |
| EU Rs        | European Union Reference Laboratories for Pesticide Residues (former CRLs) |
| FAO          | Food and Agriculture Organization of the United Nations |
| GAP          | Good Agricultural Practice |
| GC           | gas chromatography |
| GLP          | Good Laboratory Practice |
| InChiKey     | International Chemical Identifier Key. |
| ISO          | International Organisation 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) |
| LC           | liquid chromatography |
| LOD          | limit of detection |
| LOQ          | limit of quantification |
| MRL          | maximum residue level |
| MS/MS        | tandem mass spectrometry detector |
| NOAEL        | no observed adverse effect level |
| OECD         | Organisation for Economic Co-operation and Development |
| PMRA         | Pest Management Regulatory Agency |
| PRiMo        | (EFSA) Pesticide Residues Intake Model |
| QuEChERS     | Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method) |
| SANCO        | Directorate-General for Health and Consumers |
| SDL          | screening detection limit |
| SMILES       | simplified molecular-input line-entry system |
| TOF          | time-of-flight |
| TRV          | toxicological reference values |
| WHO          | World Health Organization |
Appendix A – Pesticide Residue Intake Model (PRIMo)

### Toxicological properties and MRLs for propoxur

| Commodity/group of commodities | MRLs set at the LOQ (in % of ADI) | Commodities not under assessment (in % of ADI) |
|--------------------------------|-----------------------------------|-----------------------------------------------|
| Maize/corn                     | 247.1% 1.24                      | 119.5% 21.6% 14.1%                           |
| Apples                         | 130.4% 0.65                      | 48.9% 16.9% 11.6%                           |
| Wheat                          | 121.8% 0.61                      | 39.5% 25.0% 8.4%                           |
| Wheat                          | 121.2% 0.61                      | 77.4% 6.5% 5.2%                           |
| Wheat                          | 108.8% 0.54                      | 58.6% 6.3% 6.2%                           |
| Sugar beet roots               | 106.7% 0.53                      | 45.7% 9.2% 7.3%                           |
| Potatoes                       | 89% 0.45                         | 41% 8% 7%                                 |
| Wheat                          | 82% 0.41                         | 25% 11% 9%                                |
| Soyabeans                      | 79% 0.39                         | 16% 8% 7%                                |
| Potatoes                       | 75% 0.38                         | 14% 7% 5%                                |
| Milk: Cattle                   | 75% 0.37                         | 13% 8% 8%                                |
| Potatoes                       | 73% 0.36                         | 11% 8% 7%                                |
| Soyabeans                      | 71% 0.36                         | 11% 8% 7%                                |
| Oranges                        | 71% 0.35                         | 25% 9% 4%                                |
| Apples                         | 69% 0.34                         | 25% 9% 5%                                |
| Apples                         | 67% 0.34                         | 25% 8% 5%                                |
| Wheat                          | 65% 0.32                         | 9% 7% 5%                                 |
| Apples                         | 58% 0.29                         | 34% 4% 3%                                 |
| Potatoes                       | 57% 0.28                         | 17% 6% 5%                                |
| Wine grapes                    | 42% 0.21                         | 11% 8% 5%                                |
| Oranges                        | 39% 0.19                         | 9% 5% 4%                                 |
| Wheat                          | 33% 0.17                         | 9% 3% 2%                                 |
| Tomatoes                       | 33% 0.16                         | 13% 3% 3%                                 |
| Apples                         | 32% 0.16                         | 8% 6% 4%                                 |
| Potatoes                       | 29% 0.14                         | 7% 4% 3%                                 |
| Potatoes                       | 27% 0.13                         | 6% 3% 3%                                 |
| Potatoes                       | 26% 0.13                         | 8% 2% 2%                                 |
| Bananas                        | 25% 0.13                         | 11% 2% 1%                                |
| Rye                            | 24% 0.12                         | 8% 2% 2%                                 |
| Apples                         | 19% 0.10                         | 7% 4% 2%                                 |
| Tomatoes                       | 16% 0.08                         | 7% 2% 1%                                 |

### Chronic risk assessment: JMPR methodology (IEDI/TMDI)

The estimated TMDI/NEDI/IEDI was in the range of 0% to 247.1% of the ADI. For 6 diet(s) the ADI is exceeded.

### Conclusions

Theoretical exposure assuming all food products covered by Annex I of Regulation (EC) No 396/2008 contain residues at a level equal to the LOQ of 0.01 mg/kg. Consume risk assessment not performed since TRV not proposed for propoxur.
### Acute risk assessment/children

#### Results for children

| Commodities           | MRL/Input for RA (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI | Commodities           | MRL/Input for RA (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI |
|-----------------------|--------------------------|---------------------|-----------------------|-----------------------|--------------------------|---------------------|-----------------------|
| Potatoes              | 0.01/0.01                | 1.54                | 307.52%               | Head cabbages         | 0.01/0.01                | 0.42                | 84%                   |
| Melons                | 0.01/0.01                | 1.52                | 303.37%               | Watermelons           | 0.01/0.01                | 0.41                | 84%                   |
| Peas                  | 0.01/0.01                | 1.38                | 276.98%               | Table grapes          | 0.01/0.01                | 0.34                | 84%                   |
| Oranges               | 0.01/0.01                | 1.33                | 276.98%               | Milk: Cattle          | 0.01/0.01                | 0.39                | 84%                   |
| Mik: Cattle           | 0.01/0.01                | 1.24                | 276.98%               | Swedes/rutabagas      | 0.01/0.01                | 0.34                | 84%                   |
| Watermelons           | 0.01/0.01                | 1.22                | 276.98%               | Oranges               | 0.01/0.01                | 0.31                | 84%                   |
| Apples                | 0.01/0.01                | 1.08                | 276.98%               | Pears                 | 0.01/0.01                | 0.31                | 84%                   |
| Pineapples            | 0.01/0.01                | 1.01                | 276.98%               | Potatoes              | 0.01/0.01                | 0.30                | 84%                   |
| Bananas               | 0.01/0.01                | 0.97                | 276.98%               | Pineapples            | 0.01/0.01                | 0.30                | 84%                   |
| Peaches               | 0.01/0.01                | 0.95                | 276.98%               | Yams                  | 0.01/0.01                | 0.28                | 84%                   |
| Mangoes               | 0.01/0.01                | 0.79                | 276.98%               | Apples                | 0.01/0.01                | 0.28                | 84%                   |
| Grapefruits           | 0.01/0.01                | 0.79                | 276.98%               | Cucumbers             | 0.01/0.01                | 0.28                | 84%                   |
| Table grapes          | 0.01/0.01                | 0.73                | 276.98%               | Aubergines/egg plants | 0.01/0.01                | 0.27                | 84%                   |
| Cucumbers             | 0.01/0.01                | 0.66                | 276.98%               | Mangoes               | 0.01/0.01                | 0.26                | 84%                   |
| Carrots               | 0.01/0.01                | 0.63                | 276.98%               |                       |                          |                     |                       |

#### Results for adults

| Commodities           | MRL/Input for RA (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI |
|-----------------------|--------------------------|---------------------|-----------------------|
| Sugar beets (root)/sugar | 0.01/0.12                | 1.10                | 220.3%               |
| Potatoes/fried         | 0.01/0.01                | 0.93                | 186.9%               |
| Pumpkins/boiled        | 0.01/0.01                | 0.89                | 177.4%               |
| Winter/sprouts/boiled  | 0.01/0.01                | 0.89                | 177.4%               |
| Broccoli/boiled        | 0.01/0.01                | 0.79                | 177.4%               |
| Cauliflowers/boiled    | 0.01/0.01                | 0.70                | 177.4%               |
| Escaroles/broad-leaved end | 0.01/0.01            | 0.66                | 177.4%               |
| Potatoes/dried (flakes)| 0.01/0.01                | 0.59                | 177.4%               |
| Leeks/boiled           | 0.01/0.01                | 0.57                | 177.4%               |
| Apples/boiled          | 0.01/0.01                | 0.54                | 177.4%               |
| Oranges/boiled         | 0.01/0.01                | 0.53                | 177.4%               |
| Turnips/boiled         | 0.01/0.01                | 0.51                | 177.4%               |
| Parsnips/boiled        | 0.01/0.01                | 0.51                | 177.4%               |
| Florence fennel/boiled | 0.01/0.01                | 0.45                | 177.4%               |

### Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

#### Results for children

| Commodities           | MRL/Input for RA (mg/kg) | Exposure (µg/kg bw) |
|-----------------------|--------------------------|---------------------|
| Sugar beets (root)/sugar | 0.01/0.12                | 1.10                |
| Potatoes/fried         | 0.01/0.01                | 0.93                |
| Pumpkins/boiled        | 0.01/0.01                | 0.89                |
| Winter/sprouts/boiled  | 0.01/0.01                | 0.89                |
| Broccoli/boiled        | 0.01/0.01                | 0.79                |
| Cauliflowers/boiled    | 0.01/0.01                | 0.70                |
| Escaroles/broad-leaved end | 0.01/0.01            | 0.66                |
| Potatoes/dried (flakes)| 0.01/0.01                | 0.59                |
| Leeks/boiled           | 0.01/0.01                | 0.57                |
| Apples/boiled          | 0.01/0.01                | 0.54                |
| Oranges/boiled         | 0.01/0.01                | 0.53                |
| Turnips/boiled         | 0.01/0.01                | 0.51                |
| Parsnips/boiled        | 0.01/0.01                | 0.51                |
| Florence fennel/boiled | 0.01/0.01                | 0.45                |

#### Results for adults

| Commodities           | MRL/Input for RA (mg/kg) | Exposure (µg/kg bw) |
|-----------------------|--------------------------|---------------------|
| Sugar beets (root)/sugar | 0.01/0.12                | 1.10                |
| Potatoes/fried         | 0.01/0.01                | 0.93                |
| Pumpkins/boiled        | 0.01/0.01                | 0.89                |
| Winter/sprouts/boiled  | 0.01/0.01                | 0.89                |
| Broccoli/boiled        | 0.01/0.01                | 0.79                |
| Cauliflowers/boiled    | 0.01/0.01                | 0.70                |
| Escaroles/broad-leaved end | 0.01/0.01            | 0.66                |
| Potatoes/dried (flakes)| 0.01/0.01                | 0.59                |
| Leeks/boiled           | 0.01/0.01                | 0.57                |
| Apples/boiled          | 0.01/0.01                | 0.54                |
| Oranges/boiled         | 0.01/0.01                | 0.53                |
| Turnips/boiled         | 0.01/0.01                | 0.51                |
| Parsnips/boiled        | 0.01/0.01                | 0.51                |
| Florence fennel/boiled | 0.01/0.01                | 0.45                |

### Conclusion:

The estimated short term intake (IESTI) exceeded the toxicological reference value for 27 commodities. For processed commodities, the toxicological reference value was exceeded in one or several cases. The calculation is based on the large portion of the most critical consumer group.
### Appendix B – Used compound codes

| Code/trivial name | IUPAC name/SMILES notation/InChiKey<sup>(a)</sup> | Structural formula<sup>(b)</sup> |
|------------------|---------------------------------------------------|----------------------------------|
| Propoxur         | 2-isopropoxyphenyl methylcarbamate: CC(C)Oc1ccccc1OC(=O)NC ISRUGXGCGIOQO-UHFFFAOYSA-N | ![Structural formula for Propoxur](image) |
| metabolite A     | 2-hydroxyphenyl-N-methylcarbamate: O=C(Oc1ccccc1O)NC CEHPRGMLPBMLL-UHFFFAOYSA-N | ![Structural formula for metabolite A](image) |
| metabolite B     | 2-isopropoxyphenyl-N-hydroxymethylcarbamate: CC(C)Oc1ccccc1OC(=O)NCO YCJMZNCUUBNJPT-UHFFFAOYSA-N | ![Structural formula for metabolite B](image) |
| M2               | 2-isopropoxyphenol: CC(C)Oc1ccccc1O ZNCUUYCDKVNJH-UHFFFAOYSA-N | ![Structural formula for M2](image) |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.

<sup>(a)</sup>: ACD/Name 2019.1.3 ACD/Labs 2019 Release (File version N05E41, Build 111418, 3 September 2019).
<sup>(b)</sup>: ACD/ChemSketch 2019.1.3 ACD/Labs 2019 Release (File version C05H41, Build 111302, 27 August 2019).