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STATEMENT

Statement on the assessment of quality of data available to EFSA to derive the health-based guidance values for carbendazim

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Abstract

Carbendazim (CBZ) is an active substance in plant protection products that is no longer authorised within the European Union. CBZ is classified according to Regulation (EC) No 1272/2008 as mutagenic, category 1B and toxic for reproduction, category 1B. In 2010, EFSA established consumers' health-based guidance values (HBGVs) for CBZ (ADI and ARfD). In compliance with Article 43 of Regulation (EC) No 396/2005, the European Commission asked EFSA on 1 March 2024 to carry out a follow-up qualitative assessment of the data gaps that were identified in the studies used in the framework of the assessment of the HBGVs for CBZ, in order to confirm the reliability of the existing toxicological studies and their impact for the setting of the HBGVs. By considering missing information in the extensive database and the reliability of the available toxicological studies, EFSA concluded that missing information does not prevent setting of HBGVs and that the critical effects of CBZ were investigated in studies of sufficient reliability and acceptability. Therefore, the HBGVs derived in 2010 are protective for the consumers.

KEYWORDS

carbendazim, fungicide, health-based guidance values, pesticide, risk assessment

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SUMMARY

Carbendazim (CBZ) is an active substance in plant protection products and its approval under Regulation (EC) No 1107/2009 expired on 30 November 2014. CBZ is classified according to Regulation (EC) No 1272/2008 as mutagenic, category 1B and toxic for reproduction, category 1B. In 2010, EFSA established an acceptable daily intake (ADI) of 0.02 mg/kg bw per day and an acute reference dose (ARfD) of 0.02 mg/kg bw (EFSA, 2010a). CBZ is also the main metabolite of benomyl and thiophanate-methyl.

Maximum residue levels (MRLs) are currently set for both thiophanate-methyl and for 'sum of benomyl and CBZ expressed as CBZ' at levels above the limit of analytical determination (LOD) for various commodities. In 2014, EFSA reviewed the existing MRLs for CBZ and thiophanate-methyl (EFSA, 2014). The residue definitions and MRLs derived by EFSA as the outcome of the review have not yet been implemented in the annexes to Regulation (EC) No 396/2005.

In 2020, the European Commission mandated EFSA to assess whether CBZ and thiophanate-methyl have clastogenic potential and to reconsider whether health-based guidance values (HBGVs) for consumer risk assessment (ADI and ARfD) can be derived for thiophanate-methyl and/or CBZ. In case HBGVs for consumer risk assessment could be derived for CBZ and thiophanate-methyl, EFSA was tasked to derive them, to assess the chronic and acute risk to consumers and to recommend MRLs for both active substances.

Based on the assessment of the available data, EFSA concluded that there is evidence indicating that both CBZ and thiophanate-methyl are not clastogenic but aneugenic (EFSA, 2021). EFSA confirmed the existing HBGVs for CBZ (i.e. ADI of 0.02 mg/kg bw per day and ARfD of 0.02 mg/kg bw) and set those for thiophanate-methyl at the same level (i.e. ADI of 0.02 mg/kg bw per day and ARfD of 0.02 mg/kg bw). Based on the above, MRL proposals were derived, and a consumer risk assessment was carried out. EFSA noted that, as some of the information required by the regulatory framework was found to be missing, the consumer risk assessment was considered indicative only and identified possible acute risk to consumers for some products. The outcome of the review has not yet been implemented in the annexes to Regulation (EC) No 396/2005.

As in that framework no assessment of whether CBZ and thiophanate-methyl have endocrine-disrupting (ED) properties under the new criteria established by Regulation (EU) 2018/605 was conducted, in 2022 the Commission mandated EFSA to perform that assessment and to conclude whether the toxicological reference values derived by EFSA in 2021 are expected to be protective also in this regard, or if new values should be derived, revising the consumer risk assessment and the MRLs derived by EFSA in 2021, if new toxicological reference values were needed. In the outcome of that assessment (EFSA, 2024), EFSA concluded that for thiophanate-methyl, ED criteria for thyroid (T)-modality, established by Regulation (EU) 2018/605 are met and the established HBGVs can be set and are sufficiently protective for consumers. For CBZ, the ED criteria were not met; hence no further considerations on the impact of the ED assessment on the current HBGVs were needed. Consequently, the consumer risk assessment and the MRL recommendations derived in 2021 were confirmed.

These EFSA outcomes have considered the most complete toxicological data package available: some of the studies used by EFSA to derive its conclusions for CBZ were considered to have minor deficiencies, mostly in relation to the fact that some data were generated before the Organisation for Economic Co-operation and Development (OECD) published its test guidelines (TG) for chemicals. Nevertheless, EFSA concluded that the identified deficiencies were only minor, and based on the available data, it was possible to confirm the existing HBGVs for CBZ and to derive new ones for thiophanate-methyl.

On the other hand, in September 2023, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) re-evaluated CBZ[1] and concluded that the submitted toxicological information was insufficient to allow a re-evaluation of this substance to confirm or amend the HBGVs established by JMPR in 1995 (ADI) and 2005 (ARfD). Therefore, it withdrew the current ADI and ARfD values and proposed the withdrawal of all Codex MRLs (CXLs). This is planned for discussion at the meeting of the Codex Committee on Pesticide Residues (CCPR) meeting in 2024.

During the meeting of the Standing Committee on Plants, Animals, Food and Feed – Section Phytopharmaceuticals-Pesticide Residues, that was held on 1–2 February 2024, one Member State requested additional information on the nature and seriousness of those deficiencies, noting that this would be needed by risk managers in order to proceed with the revision of the MRLs for those substances, i.e. benomyl, CBZ and thiophanate-methyl. In order to ensure that tentative MRLs derived by EFSA (2021) and confirmed in 2024 (EFSA, 2024) are safe for consumers, the European Commission asked EFSA on 1 March 2024 to carry out a follow-up qualitative assessment of the data gaps that were identified for those studies in the framework of the assessment of the HBGVs for CBZ, in order to confirm the reliability of the existing toxicological studies and its impact for the setting of the HBGVs.

The screening step to assess the completeness of the data set available for CBZ compared with the current data requirements identified several data gaps:

- An assessment of the validity of the analytical methods used in feed, body fluids and tissues and any additional matrices used in support of the toxicity studies;
- An assessment of the toxicological relevance of impurities present in the technical specification;
- An interspecies comparative in vitro metabolism study;

[1] https://www.fao.org/3/cc8226en/cc8226en.pdf (Summary Report).

- An assessment of the phototoxicity/photomutagenicity;
- An assessment of the immunotoxicity potential of CBZ;
- An updated search for the open literature (even if additional searches were performed by EFSA, they did not include all toxicological endpoints).

The missing information does not prevent the setting of HBGVs, as the fulfilment of these data would mainly influence the strength of the confidence in the HBGVs values and the uncertainty factors (UF) of 500 currently applied.

An assessment of the reliability of the studies indicates that some toxicological endpoints (short-and long-term toxicity in rats and dogs), are addressed with old studies that are not Good Laboratory Practice (GLP) or OECD TG compliant and considered of limited or supportive reliability. Nonetheless, the toxicological data package is very extensive and the critical effects of CBZ were investigated in studies of sufficient reliability and assessed as acceptable. The mode of action of CBZ is well understood. The reference points derived from these studies together with the UF applied cover the uncertainties regarding the quality of other toxicity studies of limited or supportive reliability.

On this basis and considering that worst cases have been taken into account, as well as a high UF applied, it is concluded that the HBGVs derived in 2010 are protective to consumers.

INTRODUCTION

Carbendazim (CBZ) is an active substance in plant protection products and its approval under Regulation (EC) No 1107/2009[2] expired on 30 November 2014. CBZ is classified according to Regulation (EC) No 1272/2008[3] as mutagenic, category 1B and toxic for reproduction, category 1B (ECHA, 2019e). In 2010, EFSA established an acceptable daily intake (ADI) of 0.02 mg/kg bw per day and an acute reference dose (ARfD) of 0.02 mg/kg bw (EFSA, 2010a). CBZ is also the main metabolite of benomyl and thiophanate-methyl.

Benomyl is not approved as an active substance in plant protection products under Regulation (EC) No 1107/2009 and was never assessed in the EU. Therefore, no EU health-based guidance values (HBGVs) are available and the safety of MRLs for this substance could not be assessed.

Thiophanate-methyl is an active substance in plant protection products and no longer approved under Regulation (EC) No 1107/2009 following adoption of Commission Implementing Regulation (EU) 2020/1498.[4] Thiophanate-methyl is classified according to Regulation (EC) No 1272/2008, i.e. as mutagenic, category 2 (ECHA, 2019b). In 2005, the Commission established an ADI of 0.08 mg/kg bw per day and an ARfD of 0.2 mg/kg bw (European Commission, 2005).

MRLs are currently set for both thiophanate-methyl and for 'sum of benomyl and CBZ expressed as CBZ' at levels above the limit of analytical determination (LOD) for various commodities. MRLs are set in Annexes II and III B to Regulation (EC) No 396/2005[5] for both active substances and were last modified by Commission Regulation (EU) No 559/2011.[6] Codex MRLs have been set for the sum of benomyl, CBZ and thiophanate-methyl, expressed as CBZ. In 2014, EFSA reviewed the existing MRLs for CBZ and thiophanate-methyl (EFSA, 2014). The residue definitions and MRLs derived by EFSA as the outcome of the review have not yet been implemented in the annexes to Regulation (EC) No 396/2005.

In 2020, the European Commission mandated EFSA to assess whether CBZ and thiophanate-methyl have clastogenic potential and to reconsider whether HBGVs for consumer risk assessment (ADI and ARfD) can be derived for thiophanate-methyl and/or CBZ. In case HBGVs for consumer risk assessment could be derived for CBZ and thiophanate-methyl, EFSA was tasked to derive them, to assess the chronic and acute risk to consumers and to recommend MRLs for both active substances.

Based on the assessment of the available data, EFSA concluded that there is evidence indicating that both CBZ and thiophanate-methyl are not clastogenic but aneugenic (EFSA, 2021). EFSA confirmed the existing HBGVs for CBZ (i.e. ADI of 0.02 mg/kg bw per day and ARfD of 0.02 mg/kg bw) and derived lower ones for thiophanate-methyl (i.e. ADI of 0.02 mg/kg bw per day and ARfD of 0.02 mg/kg bw, same as for CBZ). Based on the above, MRL proposals were derived, and a consumer risk assessment was carried out. EFSA noted that, as some of the information required by the regulatory framework was found to be missing, the consumer risk assessment is to be considered indicative only and identified possible acute risk to consumers for some products. The outcome of the review has not yet been implemented in the annexes to Regulation (EC) No 396/2005.

As in that framework no assessment of whether CBZ and thiophanate-methyl have endocrine-disrupting (ED) properties under the new criteria established by Regulation (EU) 2018/605[7] was conducted, in 2022 the Commission mandated EFSA to perform that assessment and to conclude whether the toxicological reference values derived by EFSA in 2021 are expected to be protective also in this regard, or if new values should be derived, revising the consumer risk assessment and the MRLs derived by EFSA in 2021, if new toxicological reference values were needed. In the outcome of that assessment (EFSA, 2024), EFSA concluded that, while for thiophanate-methyl, ED criteria for thyroid (T)-modality, established by Regulation (EU) 2018/605[8] are met, the established HBGVs are sufficiently protective for consumers. Consequently, the consumer risk assessment and the MRL recommendations derived in 2021 were confirmed.

Those EFSA outcomes have considered the most complete toxicological data package available, some of the studies used by EFSA to derive its conclusions for CBZ were considered to have minor deficiencies, mostly in relation to the fact that some data were generated before the Organisation for Economic Co-operation and Development (OECD) published its test guidelines for chemicals. Nevertheless, EFSA concluded that the identified deficiencies were only minor, and based on the available data was able to confirm the existing HBGVs for CBZ and to derive new ones for thiophanate-methyl.

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

[3]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.

[4]Commission Implementing Regulation (EU) 2020/1498 of 15 October 2020 concerning the non-renewal of approval of the active substance thiophanate-methyl, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. C/2020/7017. OJ L 342, 16.10.2020, p. 5.

[5]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.

[6]Commission Regulation (EU) No 559/2011 of 7 June 2011 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for captan, carbendazim, cyromazine, ethephon, fenamiphos, thiophanate-methyl, triasulfuron and triticonazole in or on certain products (OJ L 152, 11.6.2011, p. 1), ELI: https://data.europa.eu/eli/reg/2011/559/oj.

[7]Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine-disrupting properties. OJ L 101, 20.4.2018, p. 33.

[8]Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine-disrupting properties. OJ L 101, 20.4.2018, p. 33.

On the other hand, in September 2023, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) re-evaluated CBZ and concluded that the submitted toxicological information was insufficient to allow a re-evaluation of this substance to confirm or amend the HBGVs established in 1995 (ADI) and 2005 (ARfD). Therefore, it withdrew the current ADI and ARfD values and proposed the withdrawal of all CXLs. This is planned for discussion at the meeting of the Codex Committee on Pesticide Residues (CCPR) meeting in 2024.

During the meeting of the Standing Committee on Plants, Animals, Food and Feed – Phytopharmaceuticals-Pesticide Residues, that was held on 1–2 February 2024, one Member requested additional information on the nature and seriousness of those deficiencies, noting that this would be needed by risk managers in order to proceed with the revision of the MRLs for those substances. In order to ensure that MRLs derived by EFSA in 2021 (EFSA, 2021) and confirmed in 2024 (EFSA, 2024) are safe for consumers, EFSA was requested to carry out a follow-up qualitative assessment of the data gaps that were identified for those studies in the framework of the assessment of the HBGVs for CBZ, in order to confirm the reliability of the derived HBGVs.

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE REQUESTOR

EFSA was requested by the European Commission on 1 March 2024[9] to provide a statement according to Article 43 of Regulation (EC) No 396/2005:

- For each of the studies that were used by EFSA to derive the HBGVs for CBZ in its relevant outputs (EFSA, 2010a, 2014, 2021):
    - to implement a qualitative assessment of the identified data gaps according to the current data requirement, and their impact for the setting of the HBGVs;
    - to assess the reliability of existing toxicological studies on CBZ and its impact for the setting of the HBGVs;
    - to confirm that the derived HBGVs are sufficiently protective for consumers.

EFSA was requested to deliver the statement not later than one month from receipt of this mandate.

HUMAN HEALTH

Data

EFSA gathered all relevant information on the toxicological profile of CBZ. The sources of information for all studies were:

- the renewal assessment report (RAR) for the active substance CBZ prepared by the Rapporteur Member State (RMS), Germany, and the co-RMS, Slovenia (Germany, 2009);
- the RAR for the active substance thiophanate-methyl, precursor of CBZ, prepared by the RMS, Sweden and the co-RMS, Finland (Sweden, 2017);
- the outcome of the peer review of the pesticide risk assessment on the RMS evaluation of CBZ conducted by EFSA in the context of Commission Implementing Regulation (EU) No 844/2012[10] (EFSA, 2010a, 2010b);
- the opinions of the Biocidal Products Committee of the European Chemicals Agency on the approval of the active substance CBZ as Product Type (PT) 7 (ECHA, 2019c), PT9 (ECHA, 2019a) and PT10 (ECHA, 2019d) and respective assessment reports prepared by the evaluating Competent Authority (eCA), Germany (Germany, 2019);
- the CLH report on the proposal for harmonised classification and labelling of CBZ based on the Regulation (EC) No 1272/2008[11] (CLP Regulation), prepared by the dossier submitter Germany and respective Committee for Risk Assessment opinion (ECHA, 2019e);
- toxicological information published under REACH Registration for an estimated tonnage band use of 1–10 tonnes; the Reasoned Opinion on the toxicological properties and MRLs for CBZ (EFSA, 2021);
- the outcome of the assessment on the ED properties of the active substance CBZ in accordance with Commission Regulation (EU) 2018/605 (EFSA, 2024).
- In addition, the JMPR reports from 1995 and 2005 on CBZ establishing the ADI and ARfD respectively were also consulted.

[9] https://open.efsa.europa.eu/questions/EFSA-Q-2024-00143?search=carbendazim.

[10] 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.

[11] 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.

Methodologies

As per the terms of reference, EFSA was asked (1) to implement a qualitative assessment of the identified data gaps according to the current data requirements, and their impact for the setting of the HBGVs; (2) to assess the reliability of existing toxicological studies on CBZ and its impact for the setting of the HBGVs; and (3) to confirm that the derived HBGVs are sufficiently protective for consumers.

To address the first question, EFSA screened the available study reports with regard to the completeness of the data set compared to the current data requirements according to Commission Regulation (EU) No 283/2013[12] and checked the impact of any missing data on the setting of the HBGVs. Since the data set includes many studies of varying quality, a preliminary screening of the reliability of the studies, as assessed by the RMS during the peer review, was included to check whether the data requirements were addressed with data of (assumed) sufficient quality.

The second question was addressed by checking in more details the reliability of the data available to address key endpoints to derive the HBGVs, i.e. checking whether each relevant toxicological endpoint was investigated with sufficiently reliable data, and assess the impact on the HBGVs when the quality of the data appeared to be lower. The outcome of these two first questions was used to answer the third question in relation to the HBGVs established by the peer review in 2010 (EFSA, 2010a) and identify relative uncertainties.

It is noted that due to time constraints to deliver the current statement, EFSA did not review the scientific elements of the information reported in each study report and respective derivation of no-observed adverse effects levels (NOAELs) or lowest observed adverse effects levels (LOAELs).

ASSESSMENT

Screening step on the completeness of the data set

The available data were compared to the current data requirements according to Commission Regulation (EU) No 283/2013,[13] Section 5, and the outcome was as follows:

1. An assessment of the validity of the analytical methods used in feed, body fluids and tissues and any additional matrices used in support of the toxicity studies is not available.
2. Since the active substance is not approved at the EU level, no assessment of the potential impurities present in the technical material can be carried out. In the EFSA conclusion from 2010 two genotoxic impurities were identified: 2,3-diaminophenazine (DAP) and 3-amino-2-hydroxyphenazine (AHP). Their maximum upper levels were established at 0.0006 and 0.0005 g/kg, respectively. In addition, the genotoxicity potential of a third impurity (Code AE F037197) was inconclusive, leading to the setting of a data gap. The presence of these impurities is pending on CBZ manufacturing process.
3. Studies on absorption, distribution, metabolism and excretion in mammals: six studies were considered as giving limited to supportive evidence on the toxicokinetic properties of CBZ. They were performed before the GLP implementation and publication of the OECD test guidelines (TG 417, 1984), being conducted between 1973 and 1983. Their testing design was noted to be similar to the recommendations given in the TG 417, including two studies using intravenous (iv) administration. Another study conducted in 1990 was assessed as reliable and acceptable, it was performed according to the principles of OECD Good Laboratory Practice (GLP) as required in Council Directive 87/18/EEC[14] and successive Legislation/Regulation and OECD TG 417. This study did not include iv administration or bile cannulation investigations.
4. An interspecies comparative in vitro metabolism study is not available.
5. Acute toxicity via the oral, dermal and inhalation routes, as well as skin and eye irritation, and skin sensitisation were tested in a number of studies, many of them performed between the 70ies and 80ies. In addition, each endpoint presented at least one more recent study (e.g. from 1997) performed according to the GLP Regulation, relevant OECD TGs and assessed as reliable and acceptable.
6. No data are available on phototoxicity or photomutagenicity, or on the ultraviolet/visible molar extinction/absorption coefficient of the active substance.
7. Short-term toxicity was mainly addressed with studies performed prior to the GLP implementation and publication of OECD TGs and considered as giving limited to supplementary information. This includes four 90-day rat studies and four 90-day dog studies reported in the RAR (Germany, 2009). The testing procedures of a 1-year toxicity study in dogs from

[12]Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with 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 93.

[13]Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with 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 93.

[14]Council Directive 87/18/EEC of 18 December 1986 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances. OJ L 15, 17.1.87, p. 29–30.

1986 complied with GLP Regulation and to a great extent to the OECD TG 452 (chronic toxicity studies), and the study was assessed as acceptable.

8. In addition, two 2-year toxicity studies in dogs from 1972 and 1976 are reported in the RAR (Germany, 2009) (under long-term toxicity), both studies were conducted prior to the implementation of GLP Regulation and OECD TGs and were considered of limited reliability.
9. Several genotoxicity studies are reported in the RAR (Germany, 2009) for each relevant endpoint: 18 bacterial reverse gene mutation assays, four in vitro gene mutation tests in mammalian cells, two in vitro chromosome aberration tests and three in vivo micronucleus studies. Additional studies are reported on non-mandatory endpoints (e.g. UDS tests, sister chromatid exchange, DNA binding or dominant lethal tests) and non-test guideline compliant investigations (e.g. investigating CBZ-related spindle inhibition). The data requirements are fulfilled with at least one fully acceptable study (i.e. conducted according to GLP regulation and relevant OECD TG) for each relevant endpoint. Additional studies were retrieved for the purpose of the renewal of thiophanate-methyl (Sweden, 2017) and under the Article 43 of Regulation (EC) No 396/2005 European Commission mandate on the toxicological properties and maximum residue levels (MRLs) for the benzimidazole substances CBZ and thiophanate-methyl (EFSA, 2021).
10. Long-term toxicity and carcinogenicity were tested in rats and mice (two studies in rats and three in mice). All studies were performed prior to the implementation of the GLP Regulation and OECD TGs, nonetheless one study on each species was assessed as reliable and acceptable.
11. In the RAR (Germany, 2009), reproductive toxicity was reported in two 3-generation reproductive toxicity studies from the 70ies, neither GLP nor OECD TG compliant and considered of limited reliability or as supplementary information. An additional 2-generation reproductive toxicity study from 1992 was briefly reported in the RAR, without an assessment of its reliability or acceptability. An F1-extended two-generation reproductive toxicity study with CBZ in rats was performed in 2014 according to GLP and OECD TG 443. This study was submitted for the purpose of renewal of thiophanate-methyl (precursor of CBZ) but has not been thoroughly evaluated by the RMS (Sweden, 2017). However, it provides up-to-date information on the reproductive toxicity endpoints.
12. In the RAR (Germany, 2009), many developmental toxicity studies are reported, either with CBZ administered by the dietary route (three studies in rats and one in rabbits) or by gavage (four studies in rats and one in rabbits). Further information was retrieved from publications, including studies in rats, rabbits, mice and hamsters. Most of the studies were assessed as reliable and acceptable, even if some were performed prior to GLP implementation. In addition, a more recent developmental toxicity study in rats was submitted for the renewal of thiophanate-methyl, although not evaluated by the RMS (Sweden, 2017).
13. Delayed neurotoxicity was assessed in an acute and a 21-day studies in hens. The studies were considered to provide supplementary information. Although no study has been provided on general neurotoxicity (in rats), developmental neurotoxicity was investigated in F1 and F2 generations in the F1-extended two-generation reproductive toxicity study in rats mentioned above.
14. An assessment of the ED potential of CBZ has been performed and discussed in a peer review expert meeting (TC 118, November 2023) (EFSA, 2024).
15. Immunotoxicity was not assessed.
16. In the RAR (Germany, 2009, 2010), the literature search covered the period between 2000 and 2008. In addition, EFSA performed a screening search in PubMed on the genotoxicity potential of CBZ (EFSA, 2021) and a search for open literature to specifically address the ED potential of the active substance (EFSA, 2024).

The screening of the data retrieved from the different sources on CBZ indicates that, overall, toxicokinetics and metabolism, acute, short- and long-term toxicity as well as genotoxicity, reproductive and developmental (neuro)toxicity endpoints are addressed. Compared to the current data requirements, the following **data gaps** were identified:

- An assessment of the validity of the analytical methods used in feed (diet administration), body fluids and tissues and any additional matrices used in support of the toxicity studies;
- An assessment of the toxicological relevance of impurities present in the technical specification of CBZ;
- An interspecies comparative in vitro metabolism study;
- An assessment of the phototoxicity/photomutagenicity;
- An assessment of the immunotoxicity potential of CBZ;
- An updated search for the open literature (even if additional searches were performed by EFSA (EFSA, 2021, 2024), did not include all toxicological endpoints).

EFSA concluded that the missing information could potentially influence the HBGVs values (e.g. literature search) or on the scientific confidence in the derived values (e.g. analytical methods to ascertain whether the animals were dosed with the accurate levels of CBZ in key studies) or whether additional information on unique metabolites to humans or on immunotoxicity should be taken into consideration. Nevertheless, the missing information does not prevent the setting of HBGVs as the related uncertainties can be reflected in the applied uncertainty factor, which, in this case, was increased to 500.

Quality and reliability of key studies used to derive health-based guidance values (HBGVs) for CBZ in 2010

The HBGVs derived for CBZ (EFSA, 2010a) are reported in Table 1:

TABLE 1 Health-based guidance values (HBGVs) established during the peer review for renewal of approval (EFSA, 2010a).

HBGVs	Value	Comments
ADI	0.02 mg/kg bw per day	Based on the NOAEL of 10 mg/kg bw per day for developmental effects (high resorption rate, reduced fetal weight, skeletal variations and malformations in rat and reduced implantations, increased resorptions, reduced litter size and skeletal malformations in rabbit) and applying an UF of 500*
ARfD	0.02 mg/kg bw	Same as for the ADI and applying an UF of 500*

Abbreviations: ADI, acceptable daily intake; ARfD, acute reference dose; UF, uncertainty factor.

*It was noted that there is a margin of safety of 2500 between the reference's values and the NOEL for the induction of aneuploidy in vivo. This margin was considered adequate to cover uncertainties with regard to species differences, influences of the methodology used (i.e. endpoint for aneuploidy measured in vivo (micronucleus) less sensitive than assessed in vitro (non-disjunction)) and the possible effects of exposure conditions (i.e. single vs. repeated administration).

The leading toxicological effect of CBZ is its aneugenic potential by acting as a spindle poison, not damaging the DNA directly and for which a threshold for adverse effects is considered applicable. A threshold concentration for aneugenic activity in vitro was identified between 0.2–0.6 µg/mL and a no-observed effect level (NOEL) for aneuploidy induction in vivo at 50 mg/kg bw. The reproductive and developmental effects of CBZ were judged as a plausible consequence of the induction of aneuploidy.

During the first peer review of CBZ (European Commission, 2007), both the ADI and ARfD were derived from the developmental toxicity NOAELs in rat and rabbit of 10 mg/kg bw per day, applying an UF of 500. The margin of safety between the HBGVs and the NOEL for aneuploidy was calculated as 2500.

During the peer review for the renewal of approval procedure (EFSA, 2010a), the RMS initially proposed in the RAR (Germany, 2009) to use the 2-year dog study presenting the lowest NOAEL in the data set of 2.6 mg/kg bw per day, as point of departure to derive the ADI, applying an UF of 100. The study exhibits several drawbacks, such as the use of formulations (containing 53% and 72% CBZ) instead of CBZ, deviations from the OECD TG 452, including missing investigations, intended top dose level not reached, and reporting deficiencies. The reliability of the study was considered limited, but the co-formulants were not expected to impact on the outcome of the study and overall, the study was considered usable for the risk assessment of CBZ.

For the setting of the ARfD, the RMS proposed to retain the developmental toxicity NOAEL of 10 mg/kg bw per day as point of departure and apply an uncertainty factor (UF) of 100.

Both proposed values correspond to the HBGVs established by the JMPR (in 1995 for the ADI and in 2005 for the ARfD, for women of childbearing age).

Uncertainties on the setting of the HBGVs were identified during the per review for the renewal of approval procedure with regard to:

1. Species differences
2. Influence of the methodology used (i.e. endpoint for aneuploidy measured in vivo micronucleus (MN) less sensitive than assessed in vitro (non-disjunction))
3. Possible effects of exposure conditions (single vs repeated exposure)

On this basis, during the PRAPeR Expert Meeting 73 (16–19 March 2010), the majority of the experts agreed to maintain the HBGVs derived in 2007 by the European Commission (EFSA, 2010b).

As indicated in Table 2, short- and long-term toxicity studies are old (from the 70ies and 80ies) and therefore performed before the implementation of the GLP Regulation and OECD TGs publication. Their reliability was assessed as limited or as supplementary information, except for the 1-year toxicity study in dogs and the 2-year carcinogenicity study in mice that were considered acceptable.

TABLE 2 Reliability of short- and long-term toxicity studies on CBZ.

Study type	Year	Species tested	Material tested	GLP	OECD TG	RMS acceptability[1]
Short-term toxicity						
90-Day dietary	1973	Rat	CBZ, purity not stated	No	No, but complied to a great extent with TG 408	Limited acceptable
93-Day dietary	1973	Rat	CBZ, purity not stated	No	No, but complied to a great extent with TG 408	Limited

(Continues)

TABLE 2 (Continued)

Study type	Year	Species tested	Material tested	GLP	OECD TG	RMS acceptability[1]
90-Day gavage	1989	Rat	CBZ, 99% pure	No	No, only females, results reported only as mean, limited reporting	Limited
90-Day dietary	1968	Rat	Formulation (72.2% CBZ)	No	No, no toxicity up to highest dose tested	Supplementary
90-Day dietary	1970	Dog	Formulation (53% CBZ)	No	No, but complied to a great extent to TG 409, limited reporting	Supplementary
90-Day dietary	1972	Dog	CBZ, 99% pure	No	No, but complied to a great extent to TG 409	Supplementary
90-Day dietary	1987 (original report 1973)	Dog	CBZ, 94% pure	No	No, but complied to a great extent to TG 409, only 3 dogs/sex per group	Limited
90-Day gavage	1982	Dog	CBZ, 99% pure	No	No, only 3 dogs/sex per group, results reported only as mean, limited reporting	Supplementary
1-Year dietary	1986	Dog	CBZ, 98.8% pure	Yes	No, but complied to a great extent to TG 452	Acceptable
2-Year dietary	1972[2]	Dog	Formulations 72.2% and 53% CBZ	No	No, but complied to a certain extent to TG 453, high dose intake doubted, limited reporting	Limited
2-Year dietary	1976	Dog	CBZ, 99 & pure	No	No, but complied to a great extent to TG 452, group mean values given for both sexes together	Limited
Long-term toxicity						
2-Year dietary	1976	Rat	CBZ, 99% pure	No	No, but complied to a certain extent to TG 453, no interim sacrifice, missing investigations, limited reporting	Acceptable as scientifically valid
2-Year dietary	1972[2]	Rat	Formulations 72.2% and 53% CBZ	No	No, but complied to a certain extent to TG 453, no interim sacrifice, low number of animals for carcinogenity, missing investigations, limited reporting	Limited
2-Year dietary	1982	Mouse	CBZ, 99.3% pure	No	No, but complied to a great extent with TG 451	Acceptable
18-Month dietary	1976	Mouse	CBZ, 99% pure	No	No, but complied to a great extent with TG 451 with major deviations, limited reporting	Limited
24-Month dietary	1982	Mouse	CBZ, 99% pure	No	No, but complied to a great extent with TG 451, limited histopathology. and missing blood exams	Limited

Abbreviations: CBZ, carbendazim; GLP, good laboratory practice; RMS, rapporteur Member State; TG, test guideline.

[1]In the RAR, 2009 on CBZ.

[2]Same study.

Genotoxicity has been extensively investigated, including acceptable studies for each genotoxic endpoint; CBZ's clastogenicity and aneugenicity potential were peer reviewed recently (EFSA, 2021). Accordingly, the genotoxic potential of CBZ is considered sufficiently addressed (ref. 3.1 above).

Reproductive toxicity studies assessed in the RAR (Germany, 2009) present the same drawbacks as short- and long-term toxicity studies (see Table 3); however, a more recent F1 extended two-generation reproductive toxicity study exists that outweigh this uncertainty. This study was not fully assessed by the RMS in the thiophanate-methyl RAR as it was considered not to impact the HBGVs or overall conclusions for CBZ and did not have a direct impact on the risk assessment of thiophanate-methyl (Sweden, 2017). Nevertheless, the study was thoroughly reviewed by EFSA in 2023 under the

assessment of the ED properties of CBZ even if not specifically assessed in view of deriving a NOAEL (EFSA, 2024). In this study, no treatment-related adverse effects were seen at the lower dose level of 13.9 mg/kg bw per day, which is above the point of departure of 10 mg/kg bw per day used to derive the HBGVs in 2010. It is therefore confirmed not to impact the setting of these HBGVs.

With regard to developmental toxicity, a number of studies were assessed as acceptable, including studies conducted according to the GLP regulation and OECD TG 414. With regard to the more recent study reported in the thiophanate-methyl RAR (Sweden, 2017), this study has no impact on the derivation of HBGVs since it used much higher dose levels (between 150 and 600 mg/kg bw per day) than the established point of departure of 10 mg/kg bw per day.

TABLE 3 Reliability of reproductive and developmental toxicity studies on CBZ.

Study type	Year	Species tested	Material tested	GLP	OECD TG	RMS acceptability[1]
Reproductive toxicity						
3-Gen dietary	1972	Rat	Formulations 70% and 50% CBZ	No	No, but complied to a great extent with TG 416, missing investigation, limited reporting	Limited
3-Gen dietary	1976	Rat	CBZ, 99% pure	No	No, but complied to a great extent with TG 416, missing investigation, but core info available	Supplementary
2-Gen dietary	1992	Rat	Not stated	Not stated	Not stated No signs of toxicity up to highest dose tested (27.4/31.2 mg/kg bw per day F/M)	Not stated
EOGRT, 2-gen	2014	Rat	CBZ, 99% pure	Yes	OECD TG 443	No fully evaluated[2]
Developmental toxicity						
Dietary	1970	Rat	Formulation with 53% CBZ	No	No, but complied to a large extent with TG 414, limited reporting	Limited
Dietary	1976	Rat	Not reported	Not reported	Not reported	Not reported
Dietary	1975	Rat	CBZ, purity not stated	No	No, but mainly complied with TG 414 with minor deviations	Acceptable
Dietary	1975	Rabbit	CBZ, purity not stated	No	No, but mainly complied with TG 414, but missing investigations and low number of fetuses	Limited
Gavage	1987	Rat	CBZ, 98.8% pure	Yes	OECD TG 414	Acceptable
Gavage	1987 (original report 1976)	Rat	CBZ, purity not stated	No	No, but mainly complied with TG 414 with minor deviations (food consumption not recorded)	Acceptable
Gavage	1987 (original report 1976)	Rat	As previous study	No	No, but complied with TG 414 and follows up from previous study with only 2 dose levels	Acceptable
Gavage	1991	Rat	CBZ, >98% pure	Yes	OECD TG 414	Acceptable
Gavage	1985	Rabbit	CBZ, 98.7% pure	Yes	OECD TG 414	Acceptable
Gavage	2011	Mice	CBZ, 98% pure	No	EPA guideline (1996); deviations from OECD TG noted	No fully evaluated[2]

Abbreviations: CBZ, carbendazim; EOGRT, extended one-generation reproductive toxicity; GLP, good laboratory practice; RMS, rapporteur Member State; TG, test guideline.

[1]In the RAR, Germany, 2009 on CBZ (unless otherwise stated).

[2]From the RAR on thiophanate-methyl, Sweden (2017).

Overall, the short- and long-term toxicity in rats and dogs are the endpoints that are addressed with studies of lower reliability in the data set. Considering that the critical adverse effects of CBZ relate to endpoints that were adequately investigated, i.e. its aneugenic potential, reproductive and developmental toxicity, these weaknesses are not seen as a concern.

Uncertainties were identified by EFSA when assessing the ED potential of CBZ, such as poor reporting of testes histopathology in dogs and lack of reproducibility in studies of longer duration. The testes effects (diffuse degeneration) were

taken into consideration in the risk assessment as a worst case; therefore, this uncertainty is not expected to impact on the setting of the HBGVs.

Another uncertainty was identified concerning the different pattern of effects observed pending on the type of test substance administration in developmental toxicity studies in rats, whether administered by gavage or by the dietary route, questioning whether the effects observed were mainly due to concentrations achieved at peak blood level (C_{max}) when the test substance is administered by oral gavage. Also in this case, a conservative approach has been adopted and all adverse effects were taken into account in setting the HBGVs, independently of the route of administration; accordingly, this uncertainty doesn't impact the setting of the HBGVs.

In the biocide assessments of CBZ (PT7, PT9 and PT10), a threshold for aneuploidy induction in sperm and bone marrow is reported after gavage administration of rats, adding that this effect is likely also responsible for the developmental toxicity observed in rats and rabbits. These assessments lead to the biocidal approval for PT7 and PT10 (ECHA, 2019e). No consumer-related HBGVs were derived for the biocidal uses, such as ADI or ARfD. The HBGVs established for the PT7 and PT10 biocide uses, for the risk assessment of both professional exposure and exposure of non-professionals and general public, i.e. $AEL_{long\text{-}term}$, $AEL_{medium\text{-}term}$ and $AEL_{short\text{-}term}$, are based on the same point of departure as for the pesticides uses at 10 mg/kg bw per day from the developmental toxicity studies in rats and rabbits; a lower UF of 300 was applied, resulting in slightly higher HBGVs of 0.03 mg/kg bw per day for the three exposure pattern.

In 2021, in its guidance on aneugenicity assessment, the EFSA Scientific Committee (SC) confirmed the general existence of an underlying threshold-based mechanism for substance that are aneugenic but not clastogenic nor causing gene mutations, that includes CBZ (EFSA, 2021).

The guidance described different scenarios for the hazard and risk characterisation of aneugenic substances based on the toxicological data available. CBZ belongs to scenario 1, i.e. data-rich substances. For this scenario the guidance describes the following: *'if it has been possible to identify a reference point for aneugenicity, generally from an in vivo mammalian erythrocyte MN test using an appropriate study protocol, then this can be compared with the reference points for other effects. The reference point would preferably be identified applying the benchmark dose approach. However, even if it has not been possible to calculate a reliable BMDL, due to insufficient dose–response information, then comparison of the breakpoint (see Section 5.1) for in vivo induction of micronuclei with the reference points for other toxicity endpoints can be informative about whether aneugenicity should be viewed as the most sensitive effect, i.e. that occurring at lowest dose levels. If the reference point for aneugenicity in vivo is higher than that for another effect, HBGVs (acute and chronic) can be set up using the well-established principles (EHC 240)'*.

For CBZ, EFSA derived an overall reference point (i.e. NOEL) for aneuploidy at 50 mg/kg bw based on several in vivo MN tests (EFSA, 2010a). The critical reference point of 10 mg/kg bw per day, coming from the developmental toxicity studies in rats and rabbits, was used for setting ADI and ARfD. Therefore, the reference point for aneugenicity in the in vivo MN test is higher than that for developmental toxicity, acknowledging that aneugenicity could cause the developmental toxicity of CBZ. The approach taken for CBZ in 2010, although based on NOEL setting, is in line with the EFSA guidance, where HBGVs were based on a most sensitive endpoint, i.e. developmental toxicity. EFSA notes that the preferred dose–response analysis for setting the reference point for aneuploidy in the in vivo MN test, as suggested by the EFSA SC is a BMD modelling following the EFSA guidance (EFSA Scientific Committee, 2017). This analysis was not performed in the RAR (Germany, 2009).

EFSA considered the performance of BMD modelling on the most recent in vivo MN study (1992) for the identification of the Reference point for aneuploidy. However, when analysing the MN data set, EFSA noted that it would not fit with any of the data distribution assumptions available in the standard BMD approach (EFSA Scientific Committee, 2022), and therefore concluded that no reliable BMD analysis could be performed.

Overall, a conservative approach was taken during the peer review by applying an additional UF of 5 (overall 500) to the relevant NOAEL, to account for the uncertainties identified at the time, and it can be concluded that this assessment is still considered protective to consumers according to the state of the art.

CONCLUSIONS

The screening step to assess the completeness of the data set available for CBZ compared with the current data requirements identified several data gaps:

- An assessment of the validity of the analytical methods used in feed, body fluids and tissues and any additional matrices used in support of the toxicity studies;
- An assessment of the toxicological relevance of impurities present in the technical specification;
- An interspecies comparative in vitro metabolism study;
- An assessment of the phototoxicity/photomutagenicity;
- An assessment of the immunotoxicity potential of CBZ;
- An updated search for the open literature (even if additional searches were performed by EFSA, they did not include all toxicological endpoints).

The missing information does not prevent the setting of HBGVs, the fulfilment of these data would mainly influence the strength of the confidence in the HBGVs values and the UF applied.

An assessment of the reliability of the studies indicates that some toxicological endpoints (short-and long-term toxicity in rats and dogs), are addressed with old studies that are not GLP or OECD TG compliant and considered of limited or supportive reliability. Nonetheless the toxicological database is very extensive and the critical effects of CBZ were investigated in studies of sufficient reliability and were assessed as acceptable. The mode of action of CBZ is well understood. The reference points derived from these studies together with the UF applied cover the uncertainties regarding the quality of other toxicity studies of limited or supportive reliability.

On this basis and considering that worst cases have been taken into account, as well as a high UF applied, it is concluded that the HBGVs derived in 2010 are protective to consumers.

ABBREVIATIONS

a.s.	active substance
ADI	acceptable daily intake
AEL	acceptable exposure level
AHP	3-amino-2-hydroxyphenazine
ARfD	acute reference dose
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
bw	body weight
CBZ	carbendazim
CCPR	Codex Committee on Pesticide Residues
C_{max}	concentration achieved at peak blood level
CXL	codex maximum residue limit
DAP	2,3-diaminophenazine
eCA	evaluating Competent Authority
ECHA	European Chemical Agency
ED	endocrine disruptor
EHC	(FAO/WHO) Environmental Health Criteria
EPA	(US) Environmental Protection Agency
F1	filial generation
GLP	Good Laboratory Practice
HBGV	health-based guidance value
iv	intravenous
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).
LOAEL	lowest observed adverse effect level
LOD	limit of detection
MN	micronucleus test
MRL	maximum residue level
MS	Member States
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PT	product type (biocides)
RAR	renewal assessment report
RMS	rapporteur Member State
TG	test guideline
T	thyroid
UDS	unscheduled DNA synthesis
UF	uncertainty factor

CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

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