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Statement on the BfR opinion regarding the toxicity of 2-chloroethanol

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Abstract

In accordance with Art. 31(1) of Regulation (EC) No 178/2002, the Commission asked EFSA to provide a scientific review on the BfR opinion on the 'Health risk assessment of ethylene oxide residues in sesame seeds' (Opinion No 024/2021) regarding the toxicity of 2-chloroethanol. In addition, EFSA was asked to clarify under which circumstances the use of the MOE approach is considered appropriate. Based on the information available to EFSA, i.e. the studies assessed in the frame of the BfR opinion and additional data provided by stakeholders not assessed by BfR, EFSA considers the genotoxicity of 2-chloroethanol as inconclusive. On this basis, EFSA would not recommend setting reference points for risk assessment or health-based guidance values until the genotoxic potential of 2-chloroethanol is clarified. EFSA therefore recommends performing new in vitro gene mutation and in vitro micronucleus tests with 2-chloroethanol following the recommendations of the most recent OECD technical guidelines to clarify its genotoxic potential. If the result of any of the test is positive, the recommendations of the EFSA Scientific Committee (2011) should be followed. If the genotoxic potential of 2-chloroethanol is finally clarified and overall negative, EFSA would recommend setting the reference point for deriving health-based guidance values based on existing toxicity studies on 2-chloroethanol.

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Summary

In accordance with Art. 31(1) of Regulation (EC) No 178/2002, the Commission asks the European Food Safety Authority (EFSA) for a scientific statement on the Bundesinstitut für Risikobewertung (BfR) opinion on the 'Health risk assessment of ethylene oxide residues in sesame seeds' (Opinion No 024/2021), taking into account the studies assessed in the frame of this opinion and any other relevant available studies on the toxicity of 2-chloroethanol, not assessed by the BfR. The Commission provided separately to EFSA the additional data received from stakeholders. In addition, and as a follow up to the position presented by EFSA in the meeting of 4 October 2021, EFSA was asked to clarify under which circumstances the use of the MOE approach is considered appropriate.

EFSA noted that the BfR opinion already covers most of the data submitted by stakeholders, except for two new genotoxicity studies (i.e. ToxTracker, which is regarded as a screening assay and an *in vitro* micronucleus test) and a read-across analysis; because of the mandate time constraints, new information provided late in the procedure (i.e. in January 2022) from stakeholders has not been taken into account and a literature review has not been performed.

The assessment of the existing *in vitro* and *in vivo* genotoxicity data permitted to conclude that they are outdated and of low reliability. This was also in line with BfR opinion.

In vitro tests are indicative of positive results for apical endpoints (gene mutation and clastogenicity), while *in vivo* some indication of negative results for apical endpoints (clastogenicity) was noted. Gene mutation was however not investigated *in vivo*.

Regarding the new genotoxicity data *in vitro*, negative results in a screening assay (ToxTracker) were observed but the test is not yet validated and not measuring apical endpoints. Moreover, negative results in the micronucleus test (clastogenicity/aneugenicity) were also obtained but using a non-standard cell line. Available carcinogenicity studies on 2-chloroethanol appeared not to be suitable to assess the carcinogenic potential of 2-chloroethanol.

Concerning the read-across analysis several limitations were noted, i.e. the analysis was not fully substantiated, the reliability of experimental data on analogues was not assessed and the experimental genotoxicity data on analogues were not considered

In summary, the identified uncertainties are (i) the inconclusive genotoxicity, therefore establishing of health-based guidance values is not recommended; (ii) identifying a reference point for carcinogenicity of 2-chloroethanol is currently not possible and (iii) the read-across analysis was considered incomplete and thus, conclusions on analogues could not be confirmed based on the available data.

Based on the aforementioned data, EFSA could not conclude on the genotoxicity and carcinogenicity of 2-chloroethanol and therefore no safe level could be derived and a standard risk assessment on 2-chloroethanol could not be performed.

EFSA agreed with the BfR assumption that the genotoxic and carcinogenic potency of 2-chloroethanol is unlikely to exceed that of ethylene oxide after oral intake. BfR gave guidance on the possible risks to 2-chloroethanol by using the margin of exposure (MOE) approach. This is in line with the EFSA Scientific Committee that stated in 2005 that '*the margin of exposure approach can be applied in cases where substances that are both genotoxic and carcinogenic have been found in food, irrespective of their origin, and where there is a need for guidance on the possible risks to those who are, or have been, exposed. The Scientific Committee is of the opinion that in principle substances which are both genotoxic and carcinogenic should not be deliberately added to foods or used earlier in the food chain if they leave residues which are both genotoxic and carcinogenic in food*'. It is important to note that when it comes to genotoxic carcinogens deliberately added to food and feed (e.g. illegal use of ethylene oxide) the MOE should not be used to overrule legal requirements.

In conclusion, EFSA recommends performing new *in vitro* genotoxicity test battery using standard and updated methods. In case of reliable and negative results, establishing a health-based guidance value may be possible based on existing toxicology studies. If either of the tests is positive, follow-up genotoxicity tests according to recommendations of EFSA Scientific Committee in 2011 should be considered.

Finally, EFSA would also recommend that a comprehensive assessment is performed to complete the current statement, including a literature review and the evaluation of new data still to be assessed and produced in the future.

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Background

Ethylene oxide, formerly used as a pesticide in the EU, is no longer authorised for use as a pesticide in the European Union (EU) under Regulation (EC) 1107/2009¹ and is classified as mutagenic, carcinogenic and toxic for reproduction (category 1B) by the European Chemicals Agency (ECHA) under the classification, labelling and packaging (CLP) Regulation,² For substances with such properties, a safe threshold for consumer exposure cannot be set.

Maximum residue levels (MRLs) for ethylene oxide have been established in Regulation (EC) 396/2005³ at the limit of quantification (LOQ). Depending on the commodity, the LOQ varies between 0.02 mg/kg and 0.1 mg/kg. The residue definition for ethylene oxide provided for in that Regulation is the sum of ethylene oxide and 2-chloroethanol, expressed as ethylene oxide. This means that for the sum, the quantified level of 2-chloroethanol has to be multiplied by a molecular weight correction factor of 0.55.

In September 2020, residues of ethylene oxide have been found in many commodities of different origins and this resulted in numerous Rapid Alert System for Food and Feed (RASFF) notifications. A harmonised risk management approach regarding the detection of ethylene oxide residues in sesame seeds was agreed at the meeting of the food and feed crisis coordinators on 9 October 2020.⁴ Following the detection of ethylene oxide residues in the food additive locust bean gum (E 410), a harmonised risk management approach was agreed at the meeting of the food and feed crisis coordinators on 13 July 2021.⁵ On 4 October 2021, a meeting on ethylene oxide took place regarding regulatory and technical aspects.⁶

In many findings, it can be observed that only residues of 2-chloroethanol are found and that ethylene oxide is absent. Information has been provided by stakeholders indicating that 2-chloroethanol could be present in food not related to the illegal use of ethylene oxide as fumigant/disinfectant. In addition, stakeholders indicate that 2-chloroethanol would not be a genotoxic carcinogen as is undoubtedly the case for ethylene oxide.

On 1 September, the Bundesinstitut für Risikobewertung (BfR) issued an updated opinion on the 'Health risk assessment of ethylene oxide residues in sesame seeds' (Opinion No 024/2021).⁷ In this opinion BfR concluded that there were not enough toxicity data to assess with certainty the mutagenic and carcinogenic effects of 2-chloroethanol and stated therefore '*Further notice pending, it is hence recommended to evaluate the genotoxicity and carcinogenicity of the metabolite 2-chloroethanol in line with that of ethylene oxide*'.

At the meeting of 4 October 2021, it was concluded that it is appropriate that EFSA provides a scientific statement on this BfR opinion, taking into account the studies assessed by the BfR in the frame of this opinion and any other relevant additional available studies, including those provided by the stakeholders to the Commission, on the toxicity of 2-chloroethanol.

At the same meeting on 4 October, EFSA made a presentation on the use of the margin of exposure (MOE) approach. In the presentation, it was summarised that '*the margin of exposure approach should not be applied to genotoxic and carcinogenic substances that have been deliberately added to the food chain to conclude on (absence of) safety. The MOE approach has been developed to assess the level of concern of genotoxic and carcinogenic substances occurring in – but not deliberately added to – foods, irrespective of their origin. It is therefore not applicable to pesticides/biocides*'. In point 3.4 'Risk assessment for ethylene oxide in sesame' of the BfR opinion, the MOE approach is used to assess the health risk related to the presence of ethylene oxide in food. It is therefore appropriate that EFSA elaborates in more detail its statement the reason why the MOE approach is not appropriate for the assessment of 2-chloroethanol.

¹ 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.

² 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.

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 https://ec.europa.eu/food/document/download/fe079da2-2cef-434a-8518-cd709de3ca37_en

⁵ https://ec.europa.eu/food/document/download/5589e33e-15cb-40cc-a9b3-9acf57356ce3_en

⁶ https://ec.europa.eu/food/document/download/f7cf4445-39b0-4131-bbf4-1ca916bff945_en

⁷ <https://www.bfr.bund.de/cm/349/health-risk-assessment-of-ethylene-oxide-residues-in-sesame-seeds.pdf>

Terms of Reference as provided by the European Commission

In accordance with Art. 31 (1) of Regulation (EC) No 178/2002 the Commission asks EFSA for a scientific statement on the Bundesinstitut für Risikobewertung (BfR) opinion on the 'Health risk assessment of ethylene oxide residues in sesame seeds' (Opinion No 024/2021), taking into account the studies assessed in the frame of this opinion and any other relevant available studies on the toxicity of 2-chloroethanol, not assessed by the BfR. To be able to do so, EFSA may liaise with BfR and the European Chemicals Agency (ECHA) regarding relevant data made available under the REACH and Biocidal Products Regulations. The Commission will provide separately to EFSA the additional data received from stakeholders.

In addition, and as a follow up to the position presented by EFSA in the meeting of 4 October 2021, EFSA is asked to clarify under which circumstances the use of the MOE approach is considered appropriate.

Assessment

In order to address the Terms of Reference, EFSA reviewed the toxicological profile of 2-chloroethanol based on the BfR opinion on health risk assessment of ethylene oxide residues in sesame seeds (BfR, 2021) and clarified under which circumstances the use of the MOE approach is considered appropriate.

The BfR opinion includes sources of information such as the Australia New Zealand Food Authority (ANZFA) Full assessment report MRL for ethylene oxide in herbs and spices (2000), the Opinion of the Scientific Committee on Food on Impurities of 1,4-dioxane, 2-chloroethanol and mono- and diethylene glycol in currently permitted food additives and in proposed use of ethyl hydroxyethyl cellulose in gluten-free bread (European Commission, 2002), the US EPA assessment on 2-chloroethanol (2012), The Netherlands National Institute for Public Health and the Environment (RIVM) Risk Assessment of ethylene oxide in sesame seeds (2020), ECHA Biocide assessment on ethylene oxide and REACH registration dossier.

EFSA notes that BfR has taken into account many of the data provided by stakeholders to the European Commission, except for new information generated after the BfR review, i.e., new genotoxicity data on 2-chloroethanol and read-across analysis provided by Industry Association (Anonymous, 2021). This new information was assessed by EFSA. However, the full study report of the *in vitro* micronucleus (MN) test was not available to EFSA.

In addition, EFSA was made aware of additional toxicological information (Anonymous, 2022) on 2-chloroethanol late in its evaluation to be taken into account within the agreed deadline; further to this, EFSA did not undertake a published literature review on 2-chloroethanol due to time constraints.

1. Information on 2-chloroethanol

2-Chloroethanol (CAS 107-07-3) has a harmonised classification Acute tox 2, H300 (fatal if swallowed); Acute tox 1, H310 (fatal in contact with skin) and Acute tox 2, H330 (fatal if inhaled). ECHA confirmed that the harmonised classification for this substance has been automatically transferred to CLP from the previously existing legislation, with an Adaptation to Technical Progress when this came into force. Therefore, no CLH report or RAC opinion is available clarifying the basis of the classification and whether endpoints other than the acute toxicity ones were considered in the assessment.

The substance is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area, at ≥ 1 to < 10 tonnes per annum. It is used by professional workers and used in the laboratory chemicals, pharmaceuticals and textile treatment products and dyes.

According to the Community rolling action plan update covering the years 2021, 2022 and 2023, no evaluation of 2-chloroethanol is planned.

Regarding biocides Regulation, 2-chloroethanol is not a biocidal active substance according to ECHA databases, although there are a couple of substances metabolising into it. A Biocidal Products Committee (BPC) Opinion was adopted on 3 December 2020 for ethylene oxide (oxirane), for which 2-chloroethanol is the main metabolite.

2. Toxicological assessment of 2-chloroethanol

EFSA reviewed the toxicological profile of 2-chloroethanol based on BfR assessment (BfR, 2021) and stakeholders review (from Industry Associations) (Anonymous, 2021). EFSA notes that BfR has

already considered many of the data provided by stakeholders to the European Commission, except for new information generated after BfR review, i.e. new genotoxicity data on 2-chloroethanol and read-across analysis provided by Food Supplements Europe (FSE).

As regards **genotoxicity**, available evidence on 2-chloroethanol, mainly coming from the ECHA REACH registration dossier,⁸ raised concerns for genotoxicity *in vitro* for gene mutation and chromosome aberration but not *in vivo* for chromosome aberration after oral exposure. However, as highlighted by BfR, the available *in vivo* studies were not conducted up to current standards and have limitations. As commented by stakeholders (Anonymous, 2021), *in vitro* genotoxicity studies also have limitations. In addition, EFSA noted that a proper *in vivo* follow up for the positive results observed *in vitro* gene mutation studies is not available (e.g. transgenic rodent mutation assay). Stakeholders provided two additional *in vitro* genotoxicity studies that were negative. However, the first study is based on a test method (the ToxTracker assay) which is regarded as a screening assay combining multiple biomarkers (monitoring the activation of specific cellular signalling pathways) that can provide mechanistic insight into the genotoxic properties of chemicals, as well as oxidative stress, protein misfolding and general cellular stress (Hendriks et al., 2012; Karlsson et al., 2014). It is not currently recommended for regulatory purposes as a stand-alone assay (there is no OECD Test Guideline yet and it is not measuring apical endpoints such as gene mutation or clastogenicity). The second study, an *in vitro* MN test, used a cell line HepaRG, a non-standard cell line for the MN test, that has not been fully validated for detection of micronuclei and its use should be properly justified by demonstrating their performance in the test according to the acceptability criteria as suggested by OECD test guideline (TG) 487 (2016). In addition, EFSA also noted that although HepaRG cells express high levels of metabolising enzymes, excess glutathione (GSH) could occur in immortalised cells such as HepaRG (Xu et al., 2018, Mitchell and Russo, 1987); therefore, the negative result in the *in vitro* MN test should be taken with caution. As already considered by BfR, balance between reactive metabolite formation such as 2-chloro acetaldehyde⁹ and detoxification via GSH conjugation could play a role on the potential mutagenicity of 2-chloroethanol. These new studies reduce some of the uncertainties on the existing data package, however, given the limitations of the old and new genotoxicity studies, the genotoxic potential of 2-chloroethanol, according to current standards, should be still considered inconclusive.

As regards **carcinogenicity**, available evidence on 2-chloroethanol did not raise concerns for carcinogenicity by the dermal route. However, the route of exposure is of low relevance to assess consumer exposure (by the oral route); in addition, deviations from OECD TG 451 such as the use of only 2 dose levels and vehicle consisting of 70% ethanol – ethanol may interfere with the toxicity of 2-chloroethanol and has its own toxicity potential – make the studies unsuitable to properly assess the carcinogenic potential of 2-chloroethanol (NTP, 1985). As highlighted by stakeholders a carcinogenicity study by the oral route is available. Deviations from the OECD TG 451 include the use of only two dose levels, applications of the test substance twice weekly, only one sex investigated (females) and limited data on methods used in histopathology; details on the test substance are also missing. According to the study author 2-chloroethanol proved to be not carcinogenic under the conditions of the experimental setup (Dunkelberg, 1983). However, as concluded for the dermal studies, this test does not appear to be suitable to assess the carcinogenic potential of 2-chloroethanol.

BfR concluded that the available *in vivo* data are not suitable to waive the genotoxic effects observed *in vitro* with sufficient certainty. BfR concluded that the genotoxic and carcinogenic potency of 2-chloroethanol is not expected to exceed that of ethylene oxide after oral intake. EFSA agreed with this statement as a worst-case approach, given the uncertainties on genotoxicity as described by BfR and the differences between the two substances as highlighted by stakeholders.

Stakeholders have proposed a **read-across analysis** and identified potential analogues for that purpose, namely 1-chloro-2-propanol, 2-chloro-1-propanol and 2-bromoethanol. EFSA does not consider the read-across analysis as presented by stakeholders complete since it did not consider the genotoxicity experimental data on analogues. In addition, the read-across analysis considered metabolism similarities; however, these similarities were only described for 2-bromoethanol. This is considered crucial considering the role of metabolism on the potential mutagenicity of 2-chloroethanol. EFSA notes that 2-bromoethanol was carcinogenic at the site of contact by the oral route (Van Duuren et al., 1985) and indeed the potential alkylating properties of both 2-chloroethanol and 2-bromoethanol are not excluded in the review as presented by the stakeholders. The read-across

⁸ <https://echa.europa.eu/registration-dossier/-/registered-dossier/19389/7/7/1>. [Accessed: 15 December 2021].

⁹ 2-chloro acetaldehyde is suspected of causing cancer according to harmonised classification and labelling.

analysis, although it may be considered scientifically valid, is incomplete and brings some uncertainties into the assessment regarding the reliability of the experimental data on analogues (not assessed). EFSA highlights these groups of compounds might have differences in potency and properties despite their similarities, so it would be preferable to have, at least, good experimental genotoxicity data on 2-chloroethanol to allow a proper conclusion.

Overall, EFSA considers the genotoxicity potential of 2-chloroethanol as inconclusive¹⁰ by following an assessment according to current standards and recommended testing strategies. In the area of food and feed genotoxicity is considered a relevant toxicological endpoint per se (EFSA Scientific Committee, 2017). EFSA would not recommend setting health-based guidance values or reference points for risk assessment until the genotoxic potential of 2-chloroethanol is clarified.

EFSA recommends performing a new Ames test and a new *in vitro* MN test using a standard cell line following the recommendations of the most recent OECD TG to clarify the genotoxic potential of 2-chloroethanol. If the result of any of the test is positive, the recommendations of the EFSA Scientific Committee (2011, 2017) should be followed. If the genotoxic potential of 2-chloroethanol is finally clarified and overall negative, EFSA would recommend setting the reference point for health-based guidance values based on existing toxicity studies on 2-chloroethanol.

3. Exposure assessment – margin of exposure approach assessment

The potential consumer exposure to 2-chloroethanol as a residue should be considered *a priori* as a concern since its genotoxic and carcinogenic potential have not been clarified and a threshold for a genotoxic substance cannot be assumed. Accordingly, a health-based guidance value (e.g. tolerable daily intake, TDI) cannot be established.

As 2-chloroethanol is a degradation product of ethylene oxide in the presence of chloride, it is included in the residue definition of ethylene oxide for risk assessment as the sum of ethylene oxide and 2-chloroethanol expressed as ethylene oxide. However, it is expected that residues of ethylene oxide in food will be comparatively low due to the high vapour pressure and high reactivity of ethylene oxide. The toxicological properties of ethylene oxide have been reviewed by the ECHA RAC (ECHA, 2017) and confirmed as mutagenic and carcinogenic, classified, inter alia as Carc. 1B, H350 (may cause cancer), Muta. 1B, H340 (may cause genetic defects) and Repr. 1B, H360Fd (may damage fertility, suspected of damaging the unborn child) and implemented into legislation by ATP14. On the other hand, even though a mutagenic activity is considered plausible for 2-chloroethanol, the inconclusive genotoxicity and carcinogenicity assessment is partially related to the low reliability of the data or even lack of data.

Based on the available information, BfR concluded that the genotoxic and carcinogenic potency of 2-chloroethanol is unlikely to exceed that of ethylene oxide after oral intake. EFSA agrees that this is a reasonable assumption but noting that BfR did not conduct a formal read-across.

BfR gave guidance on the possible risks to 2-chloroethanol by using the MOE approach. This is in line with the EFSA Scientific Committee that stated in 2005 that 'the margin of exposure approach can be applied in cases where substances that are both genotoxic and carcinogenic have been found in food, irrespective of their origin, and where there is a need for guidance on the possible risks to those who are, or have been, exposed. The Scientific Committee is of the opinion that in principle substances which are both genotoxic and carcinogenic should not be deliberately added to foods or used earlier in the food chain if they leave residues which are both genotoxic and carcinogenic in food'. It is important to note that when it comes to genotoxic carcinogens deliberately added to food and feed (e.g. illegal use of ethylene oxide) the MOE should not be used to overrule legal requirements.

4. Conclusion and Recommendations

According to the information available to EFSA for this mandate, EFSA recommends performing a new Ames test and a new *in vitro* MN test with 2-chloroethanol following the recommendations of the most recent OECD TG to clarify its genotoxic potential. If the result of any of the test is positive, the recommendations of the EFSA Scientific Committee (2011, 2017) should be followed. If the genotoxic potential of 2-chloroethanol is finally clarified and overall negative, EFSA would recommend identifying a reference point for health-based guidance values based on existing toxicity studies on 2-chloroethanol.

¹⁰ It is noted that the Scientific Committee on Food, 2002 concluded that 2-chloroethanol is unlikely to be genotoxic *in vivo*.

EFSA notes that additional information was made available on 2-chloroethanol but submitted to EFSA too late during this assessment to be taken into account within the agreed deadlines. Accordingly, EFSA recommends that a comprehensive assessment is performed to complete the current statement, including a literature review and the evaluation of new data produced in the future.

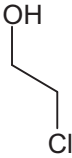

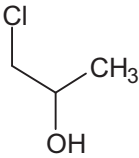
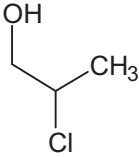
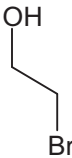
References

- Anonymous, 2021. Review Stakeholders. Informing the genotoxicity and carcinogenicity potential of 2-Chloroethanol through Structure Activity Relationships and in vitro testing approaches.
- Anonymous, 2022. Stakeholders Review. Evaluation du risque pour le consommateur de produits finis incorporant des matières premières d'origine végétale contenant des résidus d'oxyde d'éthylène et de 2-chloroéthanol.
- ANZFA (Australia New Zealand Food Authority), 2000. Full assessment report MRL for ethylene oxide in herbs and spices. Application A412, 29 November 2000, 36 pp.
- Bundesinstitut für Risikobewertung (BfR), 2021. Updated BfR opinion on Health risk assessment of ethylene oxide residues in sesame seeds, Opinion no 024/2021 issued 1 September 2021, pp. 9. <https://doi.org/10.17590/20210428-072544>
- Dunkelberg H, 1983. Carcinogenic activity of ethylene oxide and its reaction products 2-chloroethanol, 2-bromoethanol, ethylene glycol and diethylene glycol. II. Testing of 2-chloroethanol and 2-bromoethanol for carcinogenic activity. *Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene. 1. Abt. Originale B, Hygiene*, 177, pp. 269–281 (study in German).
- ECHA (European Chemicals Agency), 2017. Committee for Risk Assessment (RAC) Opinion proposing harmonised classification and labelling at EU level of ethylene oxide; oxirane, EC number: 200-849-9, CAS number: 75-21-8, CLH-O-0000001412-86-164/F adopted 22 September 2017.
- EFSA Scientific Committee, 2005. Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. *EFSA Journal* 2005;3(10):282, 31 pp. <https://doi.org/10.2903/j.efsa.2005.282>
- EFSA Scientific Committee, 2011. Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. *EFSA Journal* 2011;9(9):2379, 69 pp. <https://doi.org/10.2903/j.efsa.2011.2379>
- EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger M, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Younes M, Aquilina G, Crebelli R, Gurtler R, Hirsch-Ernst KI, Mosesso P, Nielsen E, van Benthem J, Carfi M, Georgiadis N, Maurici D, Parra Morte J and Schlatter J, 2017. Scientific Opinion on the clarification of some aspects related to genotoxicity assessment. *EFSA Journal* 2017;15(12):5113, 25 pp. <https://doi.org/10.2903/j.efsa.2017.5113>
- European Commission, 2002. Opinion of the Scientific Committee on Food on Impurities of 1,4-dioxane, 2-chloroethanol and mono- and diethylene glycol in currently permitted food additives and in proposed use of ethyl hydroxyethyl cellulose in gluten-free bread. SCF/CS/ADD/EMU/198 Final, 4 December 2002, pp. 10.
- Hendriks G, Atallah M, Morolli B, Calléja F, Ras-Verloop N, Huijskens I, Raamsman M, van de Water B and Vrieling H, 2012. The ToxTracker assay: novel GFP reporter systems that provide mechanistic insight into the genotoxic properties of chemicals. *Toxicological Sciences*, 125, 285–298. <https://doi.org/10.1093/toxsci/kfr281>
- Karlsson HL, Gliga AR, Calléja FM, Gonçalves CS, Wallinder IO, Vrieling H, Fadeel B and Hendriks G, 2014. Mechanism-based genotoxicity screening of metal oxide nanoparticles using the ToxTracker panel of reporter cell lines. *Particle and Fibre Toxicology*, 11, 41. <https://doi.org/10.1186/s12989-014-0041-9>. PMID: 25179117; PMCID: PMC4237954.
- Mitchell JB and Russo A, 1987. The role of glutathione in radiation and drug induced cytotoxicity *Br. Journal of Cancer Suppl*, 8, 96–104.
- NTP (National Toxicology Program), 1985. TR-275: Toxicology and Carcinogenesis Studies of Chloroethanol in F344/N Rats and Swiss SD-1 Mice (Dermal Studies). NTP Technical Report Series No. 275, November 1985, 196 pp.
- OECD, 2016. Test No. 487: In Vitro Mammalian Cell Micronucleus Test, OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. <https://doi.org/10.1787/9789264264861-en>
- RIVM, The Netherlands National Institute for Public Health and the Environment, 2020. Risk Assessment of ethylene oxide in sesame seeds. Front Office Food and Product Safety, 25 October 2020, pp. 15.
- US EPA (United States Environmental Protection Agency), 2012. Provisional Peer-Reviewed Toxicity Values for 2-Chloroethanol. EPA/690/R-12/007F Final. 26 November 2012, pp. 47.
- Van Duuren BL, Melchionne S, Kline SA and Seidman I, 1985. Carcinogenicity bioassays of bromoacetaldehyde and bromoethanol- potential metabolites of dibromoethane. *Teratogenesis, Carcinogenesis, and Mutagenesis*, 5, 393–403. <https://doi.org/10.1002/tcm.1770050603>
- Xu J, Oda S and Yokoi T, 2018. T. Cell-based assay using glutathione-depleted HepaRG and HepG2 human liver cells for predicting drug-induced liver injury. *Toxicology in Vitro*, 48, 286–301, ISSN 0887-2333, <https://doi.org/10.1016/j.tiv.2018.01.019>

Abbreviations

a.s.	active substance
BfR	German Federal Institute for Risk Assessment
BMDL	benchmark dose lower limit
BPC	Biocidal Products Committee
bw	body weight
CLP	classification, labelling and packaging
ECHA	European Chemicals Agency
FSE	Food Supplements Europe
LOQ	limit of quantification
MN	micronucleus test
MOE	margin of exposure
MRL	maximum residue level
MS	Member States
NOAEL	no observed adverse effect level
RAC	Risk Assessment Committee
RASFF	Rapid Alert System for Food and Feed
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	(The Netherlands) National Institute for Public Health and the Environment
SMILES	simplified molecular-input line-entry system
TDI	tolerable daily intake
TG	technical guideline

Appendix A – Chemical structure of substances

IUPAC name ^(a)	SMILES notation/InChiKey ^(b)	Structural formula ^(c)
2-chloroethan-1-ol	CICCO SZIFAVKTNFCBPC-UHFFFAOYSA-N	
Oxirane	C1CO1 IAYPIBMAFNFSPL-UHFFFAOYSA-N	
1-chloropropan-2-ol	CC(O)CCl YYTSGNJTASLUOY-UHFFFAOYSA-N	
2-chloropropan-1-ol	CC(Cl)CO VZIQXGLTRZLBEX-UHFFFAOYSA-N	
2-bromoethan-1-ol	BrCCO LDLCZOVUSADOIV-UHFFFAOYSA-N	

(a): IUPAC: International Union of Pure and Applied Chemistry.

(b): SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.

(c): ACD/ChemSketch 2021.1.3 ACD/Labs 2021 Release (File version C25H41, Build 123835, 28 August 2021).