COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from 2-MCPD, 3-MCPD and glycidol and their fatty acid esters in the diet of infants aged 0 to 12 months and children aged 1 to 5 years.

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. The SACN is examining the nutritional basis of the advice. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. Following a request from the European Commission, the Panel on Contaminants in the Food Chain (CONTAM Panel) was asked to deliver a scientific opinion on the risks for human health related to the presence of 3- and 2-monochloropropanediol (MCPD), and their fatty acid esters and glycidyl fatty acid esters (GE) in food. This risk characterisation makes use of scientific opinions from EFSA (EFSA 2016, 2018).

Background

3. 2- and 3-MCPD and their esters are contaminants of soy sauce and processed vegetable oils. They are produced as a by-product during the manufacturing process when hydrochloric acid is used to catalyse the hydrolysis of the lipids present in vegetable protein. 2- and 3-MCPD are formed when chloride ions react with glycerol. Under high temperatures, these MCPDs can then react with fatty acids in the oil to form MCPD esters, the form which is predominantly found in food.

4. Glycidyl ester (GE) is produced from fatty acids present in vegetable oil, particularly diacylglycerol (DAG) upon heating to temperatures > 200 °C which occurs during the deodorisation stage of refining.

5. 2- and 3-MCPD can form monoesters in which one of the two hydroxyl groups is esterified. They can also form diesters where both hydroxyl groups are esterified with the same or different fatty acids. Glycidol has a single hydroxyl group thus only forms monoesters. Their chemical structures are displayed in Figure 1. MCPD esters and GEs are hydrolysed to their free forms in the gastrointestinal tract.

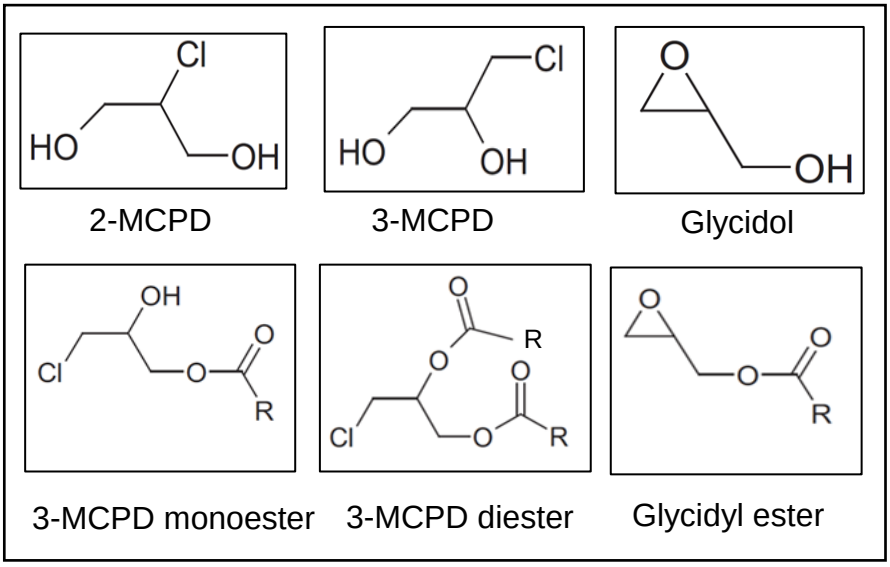


Figure 1: Chemical structures of 2- and 3-MCPD and glycidol and their esters. 3-MCPD exists as a mixture of (R)- and (S)-enantiomers that occur in a ratio of 1:1 in acid-HVP. The majority of toxicology studies concerning 3-MCPD are conducted using the racemic mixture. However renal toxicity of 3-MCPD appears to reside with the R isomer (Barocelli *et al.* 2011).

6. Maximum permitted levels of 3-MCPD are specified in Commission Regulation (EC) No 1881/2006 (EC 2006). Maximum levels for 3-MCPD in HVP and soy sauce are each 20 µg/kg. The maximum level is given for the liquid product containing 40% dry matter, corresponding to a maximum level of 50 µg/kg in the dry matter. The level needs to be adjusted proportionally according to the dry matter content of the products. In contrast to 3-MCPD, no maximum levels are laid down for 2-MCPD, 2-MCPD fatty acid esters, 3-MCPD-esters, glycidol and its esters.

Previous risk assessments

Glycidol

7. Due to 'sufficient evidence of carcinogenicity in experimental animals', glycidol was classified by the International Agency for Research on Cancer (IARC) as group 2A, 'probably carcinogenic to humans' (IARC 2000). This evaluation was based on the formation of tumours in B6C3F$_1$ mice, F344 rats (Irwin *et al.* 1996) and Syrian golden hamsters (Lijinsky & Kovatch 1992) following oral administration of glycidol. In making its overall evaluation, the working group also took into consideration that glycidol is a direct-acting DNA alkylating agent (Segal *et al.* 1990), and is mutagenic in a wide range of *in vitro* and *in vivo* test systems (reviewed by Ehrenberg & Hussain 1981).

8. A preliminary assessment of GE in refined vegetable oils was published by the Bundesinstitut für Risikobewertung (BfR 2009). The BfR concluded that current levels of infant exposure could present a health hazard. The BfR recommended that the levels of GE in vegetable oils should be reduced as far as possible.

9. As a part of a safety assessment of foods containing diacylglycerol (DAG) the Food Safety Commission of Japan (FSCJ 2015) conducted a risk assessment of glycidol and GE. FSCJ concluded that the evidence suggested glycidol to be a genotoxic carcinogen. Since genotoxicity could not be excluded, margins of exposure (MOEs) were calculated using a $BMDL_{10}$ of 1.6 mg/kg b.w./day. The exact basis of the $BMDL_{10}$ was not stated but it was derived from a two-year carcinogenicity study in which rats and mice were administered glycidol via gavage (NTP 1990). All of the GE were assumed to be converted to the equimoles of glycidol in the body. The calculated MOEs for average and maximum consumers were 17,800 and 10,900, respectively. As an alternative approach, the FSCJ also established a TDI of 1.6×10^{-3} mg/kg b.w./day by applying an uncertainty factor of 1000 to the $BMDL_{10}$. This uncertainty factor comprised a standard uncertainty factor of 100 and an additional factor of 10 for the severity of the effect (carcinogenicity). The FSCJ furthermore took a "unit risk" approach in which they estimated the exposure levels corresponding to extra risks of tumours of 10^{-4}, 10^{-5} and 10^{-6} based on simple linear extrapolation from the $BMDL_{10}$. The FSCJ recommended that GE exposure levels should be kept as low as possible according to the principle of ALARA (as low as reasonably achievable).

2-MCPD

10. To date, risk assessment bodies have not published risk assessments on 2-MCPD.

3-MCPD

11. The European Commission's Scientific Committee on Food (SCF) concluded that the increase in tumours observed in the long-term carcinogenicity study in rats (Sunahara *et al.* 1993) was the result of non-genotoxic mechanisms (SCF 1994), either through chronic hormonal imbalance (mammary gland and Leydig cell tumours in males) or sustained cytotoxicity and chronic hyperplasia (benign renal tumours in both genders). This conclusion was also reached by the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (UK COC 2000). 3-MCPD was classified by the SCF in 2001 as a non-genotoxic, threshold carcinogen (SCF 2001).

12. In 2002, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) performed a risk assessment on the presence of 3-MCPD in food (JECFA 2002). Renal tubular hyperplasia represented the critical effect in F344 rats exposed chronically via drinking water (Sunahara *et al.* 1993). Data indicating a lack of genotoxicity *in vivo* led the Committee to conclude that MCPD induces neoplasia in rats by a mechanism that does not involve DNA damage and requires exposure above a threshold dose. A provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg b.w./day was established based on a lowest observed adverse effect level (LOAEL) of 1.1 mg/kg b.w./day for renal tubular hyperplasia. An uncertainty factor of 500 was used to account for the absence of a clear NOAEL and inadequacies in the reproductive toxicity studies.

13. To investigate the possible involvement of species- and strain-specific non-genotoxic carcinogenicity, an additional two year carcinogenicity study was conducted according to OECD test guideline 451 (OECD 1981), using SD rats administered 3-MCPD in drinking water (Cho *et al.* 2008).

14. Due to 'sufficient evidence of carcinogenicity in experimental animals', the International Agency for Research on Cancer (IARC) assigned 3-MCPD to group 2B (possibly carcinogenic to humans) (IARC 2016). The working group considered that the kidney tumours observed in rats upon which this classification was based (Cho *et al.* 2008) may have been caused by the cytotoxic, metabolically formed oxalate of 3-MCPD.

15. In March 2016, the CONTAM Panel selected a $BMDL_{10}$ value for 3-MCPD of 0.077 mg/kg b.w./day for induction of renal tubular hyperplasia in male rats (Cho *et al.* 2008). The Panel derived a tolerable daily intake (TDI) of 0.8 µg/kg b.w./day through the application of an uncertainty factor of 100. In November 2016, JECFA calculated a $BMDL_{10}$ of 0.87 mg/kg b.w./day using the same data and software (Benchmark Dose Software from the US EPA) but different methodology for the BMD approach. JECFA applied an uncertainty factor of 200 (which incorporates a factor of 2 related to inadequacies in the reproductive toxicity studies), hence a TDI of 4 µg/kg b.w./day was recommended (FAO/WHO 2011).

16. Due to this scientific divergence in the establishment of the $BMDL_{10}$ reference value, and in light of the recent EFSA guidance on BMD modelling (EFSA 2017), the Panel updated its 2016 opinion for 3-MCPD and its fatty acid esters. In EFSA's revised 2018 opinion, renal tubular hyperplasia in male rats was reconfirmed as the key effect, though a new $BMDL_{10}$ of 0.20 mg/kg b.w/day 3-MCPD was obtained using PROAST software (v64.9) with model averaging. Based on this $BMDL_{10}$ value, a new group TDI of 2 µg/kg b.w./day for 3-MCPD and its fatty acid esters was established through the use of an uncertainty factor of 100 to account for intraspecies and interspecies differences (EFSA 2018).

Glycidol

ADME

17. Studies indicate an almost complete release of glycidol from GE within the human digestive tract. Therefore, the Panel assumed a complete hydrolysis of GE to glycidol following ingestion. Glycidol and its fatty acid esters are efficiently absorbed following ingestion. Metabolism of glycidol proceeds rapidly by several enzymatic pathways, including glutathione conjugation and mercapturate formation. Glycidol is predominantly excreted in urine as poorly described metabolites.

Toxicity

18. No *in vivo* data were identified for GE, therefore the Panel only considered toxicity studies involving glycidol. Glycidol induced neurotoxicity after 28 days of treatment of rats with 200 mg/kg b.w./day. Nephrotoxicity was observed in repeated dose studies in rats and mice at doses in the range 150-400 mg/kg b.w./day.

Reproductive toxicity has been noted in rats, where the LOAEL was 25 mg/kg b.w./day for a 36% reduction in epididymal sperm count.

19. Two-year carcinogenicity studies conducted by the NTP in mice (25 and 50 mg/kg b.w./day) and rats (37.5 and 75 mg/kg b.w./day) showed increased incidences of tumours in multiple organs from both sexes. Glycidol has a reactive epoxide moiety which is likely to be responsible for the genotoxic activity of the compound. There is strong evidence from *in vitro* data and some evidence from *in vivo* studies that glycidol is a genotoxic compound.

2-MCPD

ADME

20. No toxicokinetic data for 2-MCPD were identified. However, the Panel considered it unlikely that 2-MCPD exhibits the same metabolic pattern as 3-MCPD due to the different structural localisation of the chlorine atom within the molecule.

Toxicity

21. Acute median lethal dose (LD50) was estimated in one study to be 50-60 mg/kg b.w. in rats. There are limited data on the short-term toxicity of 2-MCPD. In a 28-day rat study, daily oral doses of 16 or 30 mg/kg b.w. caused severe myopathy and nephrotoxicity. The underlying mechanisms are unknown. A NOAEL of 2 mg/kg b.w./day was reported by the authors of the study. No data on long-term studies for 2-MCPD or its fatty acid esters were identified. For *in vitro* genotoxicity of 2-MCPD, only limited unpublished industry data were identified. For *in vivo* genotoxicity of 2-MCPD, a 'wing spot test' performed in *Drosophila melanogaster* showed no genotoxic effect at concentrations of 50 and 100 mM (Frei & Wurgler 1997). These genotoxicity data on 2-MCPD were too limited for the Panel to draw conclusions.

3-MCPD

ADME

22. 3-MCPD and its fatty acid esters appear to be rapidly and efficiently absorbed following ingestion, with extensive presystemic de-esterification occurring in the gastrointestinal tract of rats. In 2008, the Panel agreed with the estimate of 100% release of 3-MCPD from its esters in humans (EFSA 2008). Elimination of 3-MCPD from serum is rapid following dosing with either 3-MCPD or its dipalmitate ester. 3-MCPD is extensively metabolised by routes including glutathione conjugation and oxidation to b-chlorolactaldehyde and b-chlorolactic acid, with < 5% appearing in the urine and faeces as the parent compound. The majority of 3-MCPD is eliminated from serum within several hours of dosing with either 3-MCPD or its dipalmitate ester.

Toxicity

23. After equimolar doses of 3-MCPD and 3-MCPD dipalmitate, the biochemical changes associated with renal toxicity are similar in pattern and magnitude. This

supports the view that the esters are hydrolysed and toxicity is mediated through 3-MPCD. The Panel therefore confirmed that the toxicity of 3-MCPD fatty acid esters should be considered equivalent (on a molar basis) to that of 3-MCPD. The Panel concluded that the TDI constitutes a group TDI for 3-MCPD and its fatty acid esters (expressed as MCPD equivalents).

24. The LD50 of 3-MCPD administered by gavage was reported to be 152 mg/kg b.w. in male rats (cited in Ericsson and Baker 1970) and 191 mg/kg b.w. in ICR mice (Qian *et al.* 2007). In male rats, a single intraperitoneal (i.p.) dose of 100 mg/kg b.w. 3-MCPD produced severe renal toxicity which persisted for two weeks (Kluwe *et al.*, 1983).

25. In a two-year study, F344 rats dosed with 2 mg/kg b.w./day in drinking water showed nephrotoxicity, testicular toxicity and mammary glandular hyperplasia (males) and nephrotoxicity (females). In addition, benign tumours of the Leydig cells and mammary gland developed (Sunahara *et al.* 1993). The Panel concluded these tumours are probably irrelevant to humans as the Leydig cell tumours are highly specific to the F344 rat, and it is likely the mammary gland tumours are a consequence of the elevated oestrogen secretion arising from the testes with Leydig cell adenomas. In a recent 26-week oral study in Tg-rasH2 mice, 3-MCPD did not show carcinogenic potential, and the authors concluded that the carcinogenic potential of 3-MCPD is species-specific (Lee *et al.* 2017).

26. The Panel concluded that the kidneys and testes appear to be the main target organs of 3-MCPD. The inhibition of glycolysis by metabolites associated with the b-chlorolactate pathway was suggested as the possible nephrotoxic mechanism of 3-MCPD. Despite some positive genotoxicity tests *in vitro*, the Panel considered that there is no evidence indicating that 3-MCPD is genotoxic *in vivo*.

Health-based guidance values

Glycidol

27. The Panel considered the dose-response data to be inadequate for benchmark dose modelling as only two dose levels were administered in a two-year carcinogenicity study, where F344 rats and B6C3F1 mice were administered glycidol via gavage (NTP 1990). In cases where the dose-response data are inadequate for benchmark dose modelling, the Scientific Committee recommends the use of the T25 as the reference point, for substances that are genotoxic and carcinogenic (EFSA 2005). Therefore, the Panel derived a T25 value of 10.2 mg/kg b.w./day for peritoneal mesothelioma in male rats. This was used as the reference point for risk assessment. The T25 value is the chronic dose rate in mg/kg b.w./day, which will give 25% of the animal tumours at a specific tissue site, after specific correction for the spontaneous incidence within the standard life time of that species.

2-MCPD

28. Although the exposure data were available, EFSA did not undertake a risk characterisation for 2-MCPD and its esters due to lack of toxicological information

and insufficient data for dose-response assessments. Thus a health-based guidance value was not established for 2-MCPD.

3-MCPD

29. Based on a $BMDL_{10}$ of 0.2 mg/kg b.w./day, a TDI of 2 µg/kg b.w./day for 3-MCPD and its fatty acid esters was established through the use of an uncertainty factor of 100 to account for intraspecies and interspecies differences (EFSA 2018).

Occurrence data

30. Analytical methods validated by the American Oil Chemists' Society (AOCS) have been used for the determination of MCPD fatty acid esters and GE in edible oils. These are direct methods which quantify individual compounds, and indirect methods that quantify the MCPDs and glycidol released from their esters. Application of both direct and indirect methods in food products other than oil has been limited, and restricted mainly to indirect methods. Analytical results are therefore expressed as the parent compound (3-MCPD, 2-MCPD or glycidol) regardless of the original form (i.e. as free compound or fatty acid ester).

31. Over 80% of the 7,175 analytical results submitted to EFSA reported the analytical method and in all cases this was based on gas chromatography-mass spectrometry techniques. To estimate occurrence in food, the analytical data were categorised as follows:

1) 'soy sauce, HVP and related products' (3-MCPD only; n = 702),
2) 'oils and fats' (n = 4,754), and
3) 'other' food groups including infant formula (n = 1,719).

In the first and third categories, only the contribution from the parent compound, or fatty acid ester (in respect of infant formulae samples), respectively, was reported. The Panel noted that total occurrence of 3- and 2-MCPD may thus be underestimated in both food categories. For 'oils and fats', only the contribution from the fatty acid esters was included, however the Panel considered the contribution from the parent compound in this category to be negligible. For food groups not represented in the data set, the occurrence of 3-, 2-MCPD and glycidol was calculated from models based on estimates of the amount of oil in the products such as mayonnaise and chocolate spread.

32. For 'infants' (aged 0-12 months), the food groups 'infant and follow-on formulae', 'vegetable fats and oils' and 'cookies' were the major contributors to 2- and 3-MCPD and glycidol exposure. For 'toddlers' (aged 1-3 years), the food groups 'pastries and cakes', 'vegetable fats and oils' and 'cookies' were the major contributors to 2- and 3-MCPD and glycidol exposure. For 'other children' (aged 3-10 years) the food groups 'pastries and cakes', 'margarine and similar' and 'cookies' were the major contributors to 2- and 3-MCPD and glycidol exposure. 'Vegetable fats and oils' also contributed to 3- and 2-MCPD, and glycidol exposure. For glycidol, an additional contributor was 'fried or roast meat'.

Exposure assessment

33. EFSA's chronic dietary exposures were calculated separately for 2- and 3-MCPD and glycidol, and were assessed as mean and high (95th percentile) exposures across dietary surveys. The exposure levels showed little differences between lower bound (LB) and upper bound (UB) estimates, therefore the risk characterisation was based on middle bound (MB) estimates of exposure. The MB value is calculated by assigning a value of LOD/2 or LOQ/2 to the left-censored results.

34. For infant formula, the Panel calculated an average consumption of infant formula (diluted, ready to eat) over the period from 1 to 4 months of age to be 170 g/kg b.w./day. Occurrence values in infant formula (powder) was divided by 7.7 to account for dilution into liquid infant formula.

Glycidol

35. Exposure to glycidol referred to the parent compound, although the original form in food products was exclusively as fatty acid esters.

36. Across the dietary surveys for the age groups 'infants', 'toddlers' and 'other children', the mean exposure to glycidol was 0.3 to 0.9 µg/kg b.w./day (MB). Using P95 occurrence data resulted in a daily intake of 0.8 to 2.1 µg/kg b.w./day across dietary surveys in these age groups.

37. The mean occurrence of glycidol in diluted infant formulae was calculated to be 11.3 (10.39-12.21) µg/kg, leading to an exposure estimate of 1.9 (1.8-2.1) µg/kg b.w./day. The P95 of occurrence calculated to be 28.57 µg/kg, leading to an exposure estimate of 4.9 µg/kg b.w./day.

2-MCPD

38. The exposure assessment for 2-MCPD was based upon the level of exposure to the parent compound, regardless of the original form (i.e. as free or as ester of fatty acids), and referred to as 2-MCPD.

39. The mean 2-MCPD exposure across dietary surveys ranged from 0.2 to 0.7 µg/kg b.w./day (MB), for 'infants', 'toddlers' and 'other children'. The high exposure (P95) to 2-MCPD was 0.5 to 1.2 µg/kg b.w./day (MB) across dietary surveys in these age groups.

40. The mean occurrence of 2-MCPD in diluted infant formulae was 5.71 (4.03–7.53) µg/kg (MB (LB-UB)), leading to exposure estimates of 0.7 µg/kg b.w./day and 1.3 µg/kg b.w./day, based on LB and UB occurrence data, respectively. The P95 of occurrence of 2-MCPD in diluted formula was 9.48 µg/kg (MB = LB = UB), leading to an exposure estimate of 1.6 µg/kg b.w./day.

3-MCPD

41. The exposure assessment for 3-MCPD was based upon the level of exposure to the parent compound, regardless of the original form (i.e. as free or as ester of fatty acids), and referred to as 3-MCPD.

42. The mean exposure to 3-MCPD was 0.5 to 1.5 µg/kg b.w./day (MB) across the dietary surveys for the age groups 'infants', 'toddlers' and 'other children'. The high exposure (P95) to 3-MCPD was 1.1 to 2.6 µg/kg b.w./day (MB) across dietary surveys in these age groups.

43. The mean occurrence of 3-MCPD in diluted infant formulae was calculated to be 14.03 (14.03-14.16) µg/kg (MB (LB–UB)), leading to an exposure estimate of 2.4 µg/kg b.w./day. The P95 of occurrence value was calculated to be 19.1 µg/kg (MB = LB = UB), leading to an exposure estimate of 3.2 µg/kg b.w./day.

44. UK occurrence data for 3-MCPD (only) were reported (FSA 2010) and provided to EFSA for their European exposure assessment (EFSA 2016) (Table 1). However, only five food product categories were analysed for 3-MCPD (biscuits, bread, breakfast cereals, roasted coffee and soy sauce), therefore a UK exposure assessment based on these data alone is likely to underestimate actual exposure.

Table 1: Mean concentrations (µg/kg) of free 3-MCPD in some food groups.

Product category	**FSA (2010)**			**EFSA (2016)**		
	n	**Mean (µg/kg)**	**Max (µg/kg)**	**n**	**Mean (MB; LB-UB) (µg/kg)**	**P95 (MB; LB-UB) (µg/kg)**
Bread	30	11*	36	75	29 (23-36)	125 (118-132)
Breakfast cereals	10	3*	6	66	26 (19-33)	75 (68-82)
Soy sauce	3	2	N.D.	469	4.5 (1.1-7.9)	10 (7.6-18)

* upper bound mean (derived using LOD/2 for N.D. values)

Risk characterisation

Glycidol

45. In view of the genotoxic and carcinogenic potential of glycidol, a margin of exposure (MOE) approach was applied. MOEs were calculated by dividing the T25 value of 10.2 mg/kg b.w./day by the estimated exposure. According to EFSA guidance (EFSA 2005) 'an MOE of an order of magnitude of 10,000 or higher would not be considered of low health concern under circumstances where there were greater uncertainties, for example if the MOE was calculated using a T25, or if the reference point were based on a poor animal database'. When the reference point is based upon T25 data it is considered that the MOE should be 2.5 times higher than an MOE based upon $BMDL_{10}$ data, i.e. 25,000 (Dybing *et al.* 2008). Based on this consideration, the Panel concluded that an MOE of 25,000 or larger would be of low health concern.

46. MOEs for glycidol were calculated by dividing the point of departure (T25 of 10.2 mg/kg b.w./day) by the estimated European chronic exposures.

47. For ‘infants’, ‘toddlers’ and ‘other children’, MOE estimates for the mean dietary exposures ranged from 34,000 to 11,300. The MOE for high (P95) exposure ranged from 12,800 to 4,900.

48. Scenarios of exposure in infants receiving formula only resulted in a MOE of 5,400 (5,700-4,900) (MB (LB-UB)) for the mean occurrence and 2,100 for the P95 of occurrence.

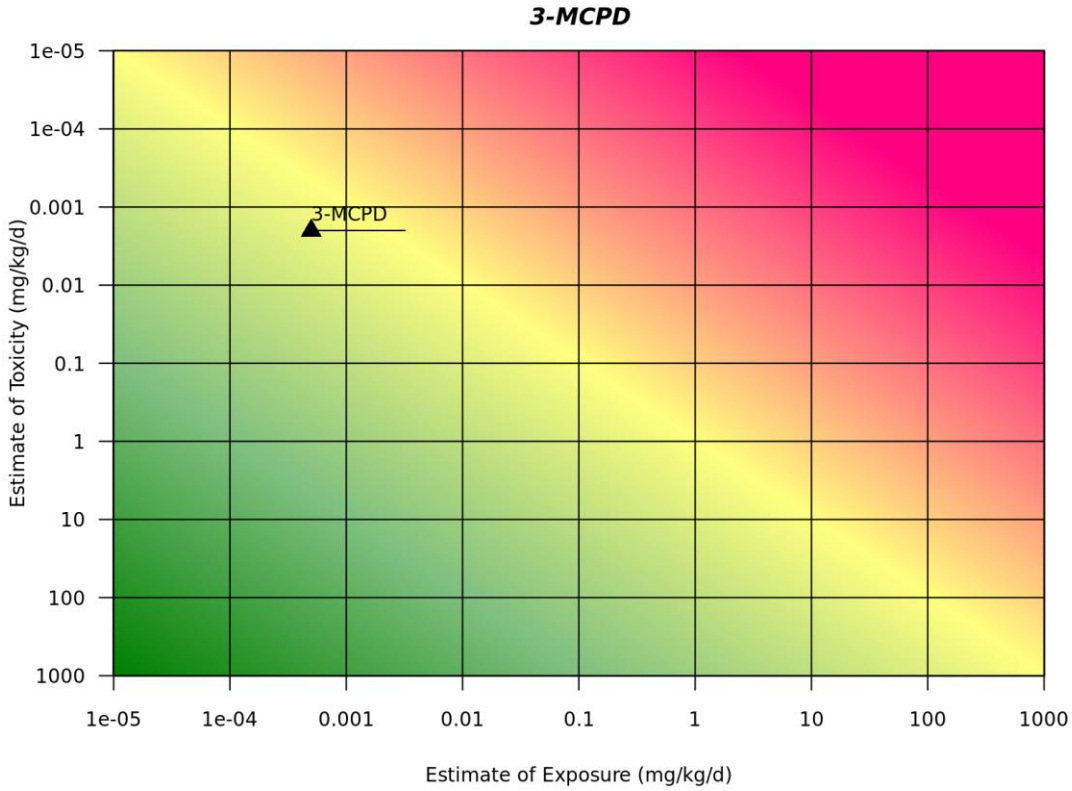
3-MCPD

49. The Panel noted that the P95 exposures for infants, toddlers and other children were up to 130% of the TDI of 2 µg/kg b.w./day. For infants receiving infant formulae, exposures were 120% (mean occurrence value) and 160% (P95 occurrence value) of the TDI.

50. The Panel recommended the acquisition of additional scientific data to address several uncertainties. These included studies on long-term toxicity and mode and action of 2-MCPD. For 3-MCPD, more data should be generated on developmental and reproductive toxicity following long-term exposure. Further studies on the rates and degree of de-esterification and the metabolic fate for 2- and 3-MCPD fatty acid esters and GE were also recommended.

<u>The RISK21 matrix</u>

51. The RISK21 matrix was developed under a program of the Health and Environmental Sciences Institute as a highly visual method of assessing risk using exposure and hazard information. Figure 2 shows the range (MB-P95) of estimated European exposures for infants receiving infant formulae, other infants, toddlers and ‘other children’ to 3-MCPD in the diet. 3-MCPD is situated at the matrix intersect indicating a marginal risk of adverse health effects.



Conclusions

52. EFSA's MOE values for infants, toddlers and 'other children' with respect to glycidol exposure appear to be of concern, and indicate a health risk.

53. EFSA's exposure values for infants receiving infant formulae, and for other infants, toddlers and 'other children' at the 95th percentile with respect to 3-MCPD exceed the TDI, and thus indicates a potential concern for the estimated chronic dietary exposures.

Questions on which the views of the Committee are sought

54. Members are invited to consider the following questions:

i) Can it be assumed for 2- and 3-MCPD and glycidol that European dietary exposure estimates are representative of UK exposures? If so, does the Committee consider the estimated exposures to be of concern?
ii) Do Members agree with EFSA's risk assessment approach for 2- and 3-MCPD and glycidol?
iii) Can a risk be characterised for 2-MCPD?

Secretariat

May 2019

References

Barocelli E., Corradi A., Mutti A. *et al.* (2011). Comparison between 3-MCPD and its palmitic esters in a 90-day toxicological study. Scientific report CFP/EFSA/CONTAM/2009/01. Available online: http://www.efsa.europa.eu/en/supporting/pub/187e.htm

BfR (2009). Initial evaluation of the assessment of levels of glycidol fatty acid esters detected in refined vegetable fats. Opinion No 007/2009.

Cho W.S., Han B.S., Nam K.T. *et al.* (2008) Carcinogenicity study of 3-monochloropropane-1,2-diol in Sprague-Dawley rats. *Food and Chemical Toxicology* **46:** 3172-3177

EC (2006) Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. OJ L 364, 20.12.2006, p. 5-24.

EFSA (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 J.* **282:** 1-31

Dybing E., O'Brien J., Renwick A.G. *et al.* (2008). Risk assessment of dietary exposures to compounds that are genotoxic and carcinogenic – an overview. *Toxicology Letters* **180:** 110-117

EFSA (2008) Statement of the Scientific Panel on Contaminants in the Food chain (CONTAM) on a request from the European Commission related to 3-MCPD esters.

EFSA (2016) Risks for human health related to the presence of 3- and 2-monochloropropanediol (MCPD), and their fatty acid esters, and glycidyl fatty acid esters in food. *EFSA Journal* **14(5):** 4426

EFSA (2017) Update: use of the benchmark dose approach in risk assessment. *EFSA Journal* **15(1):** 4658

Ehrenberg L. & Hussain S. (1981) Genetic toxicity of some important epoxides. *Mutat. Res.* **86:** 1-113

FAO/WHO (2011). WHO Food Additives Series 74. Safety evaluation of certain contaminants in food. Prepared by the eighty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Available at: https://apps.who.int/iris/bitstream/handle/10665/276868/9789241660747-eng.pdf?ua=1#page=673%22%3E

Frei F. & Würgler F.E. (1997) The vicinal chloroalcohols 1,3-dichloro-2-propanol (DC2P), 3-chloro-1,2-propanediol (3CPD) and 2-chloro-1,3-propanediol (2CPD) are not genotoxic in vivo in the wing spot test of Drosophila melanogaster. *Mutation Research* **394:** 59–68

FSA (2010). Survey of acrylamide, furan, 3 monochloropropane-1,2-diol (3-MCPD) and ethyl carbamate in UK retail products: Year 3 summary report (January 2009 – December 2009). Unpublished report.

FSCJ (2015). Considerations on glycidol and its fatty acid esters in foods. Risk assessment report – Novel Foods and Food Additives FS/185/2015. Available at: http://www.fsc.go.jp/english/evaluationreports/others/annex_glycidol_26-52.pdf

IARC (2000). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 77. Lyon, France: International Agency for Research on Cancer. pp. 469-486

IARC (2016). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 101. Lyon, France: International Agency for Research on Cancer. pp. 349-374

Irwin R.D., Eustis S.L., Stefanski S. *et al.* (1996) Carcinogenicity of glycidol in F344 rats and B6C3F1 mice. *J. appl. Toxicol.* **16:** 201-209

JECFA (2002). Evaluation of certain food additives and contaminants (Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 909

Kluwe W.M., Gupta B.N. & Lamb J.C. (1983). The comparative effects of 1,2-dibromo-3-chloropropane (DBCP) and its metabolites, 3-chloro-1,2-propaneoxide (epichlorohydrin), 3-chloro-1,2-propanediol (alphachlorohydrin), and oxalic acid, on the urogenital system of male rats. *Toxicology and Applied Pharmacology* **70:** 67-86

Lee B.S., Park S.J., Kim Y.B. *et al.* (2017) Twenty-six-week oral carcinogenicity study of 3-monochloropropane-1,2-diol in CB6F1-rasH2 transgenic mice*. Arch Toxicol.* **91(1):** 453-464

Lijinsky W. & Kovatch R.M. (1992) A study of the carcinogenicity of glycidol in Syrian hamsters. *Toxicol. ind. Health* **8:** 267-271

NTP (1990). Toxicology and carcinogenesis studies of glycidol (CAS No. 556-52-5) in F344/N rats and B6C3F1 mice (gavage studies). Technical Report Series No. 374. National Institutes of Health Publication No. 90-2829. Research Triangle Park, NC.

OECD (1981). OECD Guidelines for the Testing of Chemicals/Section 4: Health Effects. Test No. 451: Carcinogenicity Studies. OECD Publishing.

Qian G., Zhang H., Zhang G. *et al.* (2007). Study on acute toxicity of R, S and (R,S)3monchloropropane1,2diol. Journal of Hygiene Research 36: 137-40

SCF (1994). Opinion on 3-Monochloropropane 1,2-diol (3-MCPD). Expressed 16 December 1994. Reports of the Scientific Committee for Food (thirty-sixth series).

SCF (2001). Opinion on 3-monochloro-propane-1,2-diol (3-MCPD), Updating the SCF opinion of 1994 adopted on 30 May 2001. European Commission, Brussels. Available online: http://ec.europa.eu/food/fs/sc/scf/out91_en.pdf (accessed October 2010).

Segal A., Solomon J.J. & Mukai F. (1990) *In vitro* reactions of glycidol with pyrimidine bases in calf thymus DNA. *Cancer Biochem. Biophys.* **11:** 59-67

Sunahara G., Perrin I. & Marchessini M. (1993). Carcinogenicity study on 3-monochloro propane 1,2-diol (3-MCPD) administered in drinking water to Fischer 344 rats. Report No RE-SR93003, Nestec Ltd, Research and Development, Switzerland

UK COC (2000). Annual report 2000. Available online: http://cot.food.gov.uk/sites/default/files/cot/cotcomcocrep_coc.pdf