Joint Statement by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) and the Joint Expert Working Group on Food Contact Material (FCMJEG)

Safety assessment of tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE) for use in coating in canned food packaging materials.

Summary

1. Tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE) is a mixture of mono- and diglycidyl ether and TMBPF-DGE oligomers, derived from the reaction of tetramethyl bisphenol F (TMBPF) with epichlorohydrin. TMBPF-DGE is further processed to form an epoxy resin and polymer dispersion, which is then used as a component in coatings in canned food packaging materials, in contact with all food types (beverages included).

2. TMBPF-DGE contains epoxy (glycidyl) groups and as such is intended to be reactive. However, reactivity is negligible in the finished (cured) coating where it is incorporated into the polymer backbone. While TMBPF-DGE derived epoxy groups remaining in the resin may react with food constituents, no interactions with food substances after polymerisation are anticipated.

3. A worst-case approach was applied using extraction and quantification of TMBPF-DGE, its hydrolysis products and the total number of epoxy groups to assess possible exposure. Migration into acetonitrile was considered a worst case-scenario.

4. When estimating the worst-case dietary exposure to TMBPF-DGE, the hydrolysis and chlorinated products that form during the manufacturing process and application to light metal food packaging coating materials need to be considered. Hence, all TMBPF-DGE monomer derivatives were included in the total concentration used in the dietary exposure assessment.

5. TMBPF-DGE was genotoxic in vitro but while uncertainties remain over the potential ability to induce polyploidy, TMBPF-DGE was overall considered negative for mutagenicity or genotoxicity in vivo. However, when considering the other toxicological endpoints, Members of the FCMJEG and COT did not think it appropriate to formalise a health-based guidance value (HBGV) due to the lack of a long term/chronic toxicity study and other database deficiencies. The available 28-day study, while informative, did not include all the endpoints in a long term/chronic study.

6. Overall, when considering all available information, the available data did not identify a safety concern for the usage of TMBPF-DGE in can coatings. Hence, the Committees did not see any scientific reason to apply restrictions to the usage of TMBPF-DGE.

Introduction

7. Towards the end of 2021 the UK Food Standards Agency (FSA) policy team received a request by the food contact can coating sector to assess the suitability of tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE) for use in coatings in canned food packaging materials.

8. EFSA had not carried out an assessment of TMBPF-DGE and this necessitated national authorities to consider the safety and use of TMBPF-DGE as an epoxy in can coatings. In 2022, the Dutch Authorities included TMBPF-DGE in their revision of the Dutch Commodities Act (Warenwet), allowing it to be used as a coating in canned food packaging subject to specific restrictions. In accordance with mutual recognition principles, goods lawfully placed on the market within an EU member state can be freely placed on the market within Northern Ireland (NI). This does not apply to Great Britain (GB), which would have to reach its own conclusion. TMBPF-DGE is being suggested as a possible replacement for bisphenol A (BPA) in can coatings, with several global brands already marketing cans coated with TMBPF-DGE-based polymers in the European Union (EU). Manufacturers are now intending to apply the coating to cans destined for the GB market and a decision is therefore required to determine whether TMBPF-DGE should be allowed to be used in the GB market under similar conditions.

9. Given that there is no legislative framework in place for the assessment of substances in can coatings nor the ability to create or amend a positive list at present, the suitability of TMBPF-DGE was assessed outside the FSA/FSS (Food Standards Scotland) regulated products approvals process. The FSA policy team therefore does not anticipate formal authorisation of TMBPF-DGE but would take into account the finalised risk assessment in their risk management considerations. The objective will be to ensure that it appropriately sets out operator requirements and expectations.

10. The information provided to the FSA on TMBPF-DGE was considered by the Joint Expert Group on Food Contact Materials (FCMJEG), the Committee on Toxicity of Chemicals, Consumer Products and the Environment (COT) and the Committee on Mutagenicity (COM), for their specific expertise.

Assessment of non-toxicological data

Identity of substance

11. The substance is a non-defined liquid mixture, with oligomeric and monomeric units, and the chemical name phenol, 4,4’methylene bis-2,6-dimethyl-, polymer with

2-(chloromethyl)oxirane. The trade name is reported as diglycidyl ether of tetramethyl-bisphenol F – aromatic diglycidyl ether (TMBPF-DGE).

12. TMBPF-DGE is produced by the reaction of tetramethyl bisphenol F (TMBPF) with epichlorohydrin, which results in a mixture of bis(3,5-dimethyl-4-hydroxyphenyl)methane bis(2,3-epoxypropyl)ether, the major component, oligomers (due to the reaction of one or both of the epoxy groups), the dimer, trimer and tetramer (all bi-functional epoxy) of TMBPF-DGE and minor quantities of other reaction products. Hydrolysis of the epoxy group during an aqueous washing step in the reaction may occur.

13. The water content of TMBPF-DGE was < 0.05% and the residual content of epichlorohydrin and sodium were 0.79 mg/kg and 3.6 mg/kg, respectively.

14. The residual content of TMBPF was 0.77 µg/kg.

15. Formation of a TMBPF-DGE containing oligomer may occur during the synthesis of the resin or during the migration process if an oxirane/epoxide functional group on a linear oligomer reacts with a free hydroxyl group. It is possible that the cyclic oligomers are not incorporated into the cured polymer structure and hence migrate more readily. The reaction does not involve a loss or addition of mass; therefore, the linear and cyclic forms will have the same mass.

16. The submitted information considered that 93% of the resin and components cannot form a cyclic structure due to the length of the molecules. TMBPF-DGE by itself is too short, even if one of the epoxy groups is hydrolysed. A linear dimer of TMBPF-DGE with at least one epoxy group and one diol end group could theoretically form a cyclic dimer. The data provided showed that any cyclic substances were present at low (non-detectable) levels.

Physical and chemical properties

17. TMBPF-DGE is liquid at room temperature (RT). No melting point was cited.

18. No data were available on a boiling point or decomposition temperature.

19. TMBPF-DGE is soluble in water at 1.26 ± 0.1 mg/L at 20°C. The octanol/water partition coefficient (Log $P_{o/w}$) is 4.47 at 25°C. As demonstrated by the Log $P_{o/w}$ TMBPF-DGE would also be expected to be soluble in organic solvents, such as ketones, glycols, alcohols and aromatics.

20. TMBPF-DGE contains epoxy groups and as such is intended to be reactive. However, reactivity is negligible in the finished (cured) coating where it is incorporated into the polymer backbone. Hence, the submitted documentation considered the substance to be stable under the final conditions of use. While epoxy groups of any remaining TMBPF-DGE may react with food constituents no interactions with food substances are anticipated after polymerisation.

21. Epoxy groups are known to be hydrolysed into the diol components when reacted with water. No test on hydrolysis was performed but TMBPF-DGE was assumed to produce the same hydrolysis and diol components as listed under Annex I of Regulation (EC) No 1895/2005 for bisphenol A diglycidyl ether (BADGE).

Characterisation of substance after incorporation in FCM

22. TMBPF-DGE is a mixture of the mono- and diglycidyl ethers and TMBPF-DGE oligomers which are then processed to form an epoxy resin, copolymerised with acrylic-based monomers in water, forming a polymer dispersion. The epoxy resin/polymer dispersion then forms part of the final can coating material intended for food contact applications.

23. The final coating is meant as an internal protection coating in food can bodies and can end coatings (e.g., aluminium) in contact with all types of food, including beverages.

24. As a worst case the coated cans and can ends are intended for sterilisation at a maximum temperature of 130°C for 1 hour, followed by long term storage (> 6 months) at room temperature (RT).

25. The surface to volume (S/V) ratio would vary from article to article. In general, the conventional S/V ratio of 6 dm^2/kg would be applicable to small cans, for larger cans this would represent a worst-case scenario. For can ends, the actual S/V ratio would be less than the conventional 6 dm^2/kg. Coating on metal used for can ends would not be likely to exceed 12.4 g/m^2.

Migration

26. A worst-case approach was applied using, as a proxy for overall migration, extraction into olive oil and acetonitrile, and quantification of TMBPF-DGE, its hydrolysis products and the total number of epoxy groups.

27. The sum of all compounds migrating out of the coating (overall migration) into olive oil was < 2.0 mg/dm^2 or < 12 mg/6 dm^2.

28. The sum of all compounds migrating out of the coating (overall migration) into acetonitrile was 4.9 mg/dm^2 or 29.4 mg/6 dm^2.

29. The overall migration into acetonitrile was greater than the overall migration into olive oil and both the FCMJEG and COT agreed that acetonitrile provided the worst-case extraction of TMBPF-DGE and hence would provide the worst-case migration, with a degree of conservativism of at least 2.5-fold.

Quantification and identification of migrating oligomers and reaction products

30. The final coating, while in contact with food, may release residual monomers or additives, but also non-intentionally added substances (NIAS) such as oligomers and reaction products of ingredients or impurities.

31. Thus, the substances in the acetonitrile extract were further examined by liquid chromatography time of flight mass spectrometry (LC-ToF-MS) and, according to the documentation provided, the majority were found to be associated with components of the manufacturing process or the final coating. Only three were directly associated with TMBPF-DGE. The total amount of TMBPF-DGE related oligomers plus substances not identified amounted to 2.1 mg/6 dm^2. This includes substances that were present at a low level (< 50 µg/6 dm^2).

32. The sum of all compounds migrating from the coating (overall migration) showed that extraction in acetonitrile represented a worst-case scenario and is approximately 2.5-fold greater than extraction in olive oil under worst-case conditions. If this factor were applied to the specific extraction value for TMBPF-DGE and related substances of 2.1 mg/6 dm^2, then the migration of TMBPF-DGE and related substances from the coating would be approximately 1 mg/6 dm^2.

33. The submitted documents further provided an analysis of potential cyclic oligomers in the final can coating, with substances that may contribute to the quantity of cyclic oligomers. Substances that had a database match for an oligomer with a free oxirane group and/or masses with more than one peak in the extracted ion chromatograms would have the potential to have linear and/or cyclic isomeric structures. No substances (with a molecular weight < 1000 Dalton) were detected, other than those identified and quantified previously.

Residual content

34. The toxicologically active part of TMBPF-DGE is the oxirane ring (C_2H_3O) and as part of the curing process these groups are meant to react and hence would be inactivated. However, as residual amounts may remain, the final coating may contain free TMBPF-DGE with the oxirane ring intact or a range of oligomers that may contain one or more oxirane rings.

35. The residual oxirane functionality in acetonitrile extracts was 29 µg/6 dm^2, determined by nuclear magnetic resonance (NMR) spectroscopy. The submitted documentation assumed that the worst-case migration would be identical to the extracted quantity. If the surface/volume (S/V) ratio was reduced, then the worst-case migration would decrease proportionally. This would be the case for many can-end applications.

36. The total residual content of TMBPF-DGE and its hydrolysis and chlorinated products (TMBPF-DGE.H_2O, TMBPF-DGE.$2H_2O$, TMBPF-DGE.HCl, TMBPF-DGE.2HCl and TMBPF-DGE.H_2O.HCl) in the final cured coating was 92.8 µg/6 dm^2 (sum of all compounds), TMBPF was detected at 0.77 µg/6 dm^2. Analysis was by liquid chromatography coupled to mass spectrometry (LC-MS/MS). The potential hazard of TMBPF-DGE stems from the oxirane/epoxy function. Neither TMBPF nor TMBPF-DGE.$2H_2O$ have an epoxide functional group and are therefore considered less reactive and not of toxicological concern.

37. The assessment focuses on TMBPF-DGE alone and substances associated with components of the manufacturing process, or the final coating are not directly relevant. To produce the epoxy resin TMBPF-DGE can be reacted with any authorised monomer. The final product/can coating must therefore comply with the specific migration limits (SMLs) for the respective compounds.

38. Thus, the total residual content of TMBPF-DGE, including all monomer derivatives (92.8 µg/6 dm^2) was used in the submitted documents as a worst-case dietary concentration for human exposure considerations.

Assessment of toxicological data

Genotoxicity

39. Genotoxicity testing was performed with the epoxy resin (ER) of TMBPF-DGE, not TMBPF-DGE itself.

40. While TMBPF-DGE ER was clearly positive for clastogenicity and gene mutation in vitro, the in vivo bone marrow micronucleus (MN) test, a follow-up for clastogenicity, was negative. All three Committees agreed that the available (although limited) toxicokinetic data supported adequate exposure of the bone marrow under the test conditions. TMBPF-DGE, mostly as its hydrolysis product, was present in the blood and hence was assumed to have reached the bone marrow, which is a well perfused tissue.

41. An in vivo spermatogonial chromosomal aberration test was considered negative for chromosomal aberrations; however, the data did show an increase in polyploidy. While the Committees considered this unlikely to be a biologically relevant effect, given the polyploidy occurred at high concentrations (2 g/kg bodyweight (bw)) at 48 hours only and that the bone marrow assay did not show an increase in MN, uncertainty over the data and significance of the potential polyploidy remained.

42. There was no evidence from the available data for positive results in the in vivo Comet data, as a follow up to the in vitro gene mutation findings. However, there were uncertainties over the data as the studies and results were of varying quality. While liver Comet data were negative, the duodenum data showed a statistically significant decrease in % tail intensity (TI). Decreases in %TI are widely acknowledged to occur if there are DNA-DNA or DNA-protein crosslinks. However, clouds (also known as ghosts or hedgehogs) were present across all groups, especially the vehicle control group. Clouds indicate heavily damaged cells and show extensive DNA migration that cannot be reliably quantified by the software used to measure the comets. The aetiology of clouds is unknown but is indicative of poor quality cell suspensions and slide quality, especially when levels of clouds above 20 – 30% are recorded in the vehicle controls. Hence, all three Committees regarded the duodenum data as uninterpretable. While the effect detected was most

likely the result of processing issues, Members could not entirely exclude cross-linking based on the data provided.

43. Given the large number of in vivo studies (and data available) all three Committees did not consider a transgenic assay necessary at this stage of the assessment, and it would be in contradiction of the principles of the 3Rs (Replacement, Reduction, Refinement).

44. While some uncertainties remain, specifically around the significance of the potential polyploidy, the data provided a large margin of safety and overall, the Committees agreed that it is unlikely that there would be a risk to human health from any mutagenic effect of TMBPF-DGE.

General toxicity

45. Given the above conclusion on genotoxicity, the FCMJEG and COT considered whether the risk assessment should be based on the general toxicity data.

46. Chronic toxicity/carcinogenicity and reproduction/developmental toxicity studies were not available. However, a combined short-term repeated dose toxicity study with reproductive/developmental toxicity screening was provided with the submitted documentation. Males were exposed for 29 days, i.e. 2 weeks prior to mating, during mating, and up to the day prior to scheduled necropsy. Females were exposed for 38 - 56 days, i.e. 2 weeks prior to mating, during mating, during post-coitum, and during at least four days of lactation (up to the day prior to scheduled necropsy). Pups were not treated and terminated on postnatal day (PND) 5 - 7.

47. At 100 and 300 mg/kg, all animals survived the full study duration, animals in the 1000 mg/kg dosing group were terminated before mating commenced due to signs of toxicity/ill health. There were parental effects on the liver and kidney at doses of ≥ 300 mg/kg bw per day. However, the authors of the submitted documentation considered the effects of equivocal toxicological significance as they were not accompanied by histopathological signs of adversity and the only change in clinical chemistry was a less than 2-fold increase in serum enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) at 300 mg/kg bw per day in females only. The study report identified a parental no observed adverse effect level (NOAEL) of 100 mg/kg bw per day and reproductive and developmental NOAELs of at least 300 mg/kg bw per day based on the reported effects.

48. Members of the FCMJEG and COT concluded that the available data did not indicate any reproductive or developmental effects at a dose of 300 mg/kg bw per day or raise any concerns with a parental NOAEL of 100 mg/kg bw per day.

49. The endocrine data available for TMBPF-DGE ER, while not a requirement for the assessment, were of good quality and largely negative. Weak positive results were reported in an in vitro assay for induction of estradiol synthesis, an assay which the Committees noted, tended to be overly sensitive and hence can produce positive

results that are not biologically relevant. The results were just above that required for a positive “call” in the OECD test guideline where a 1.5-fold change is considered positive. No comparable activity was observed in an appropriate in vivo follow-up assay.

Exposure Assessment /Risk characterisation

50. As humans are unlikely to be exposed to TMBPF-DGE and its related derivatives from any other source than food packaging coating materials, the exposure assessment provided to the FSA was based on oral exposure resulting from food packaging applications.

51. When estimating the worst-case dietary exposure of TMBPF-DGE, the hydrolysis and chlorinated products that form during the manufacturing process and application of light metal food packaging coating materials need to be considered. Hence, in an effort to ensure the most conservative migration calculation, all TMBPF-DGE monomer derivatives were included in the migration sum, including TMBPF-DGE.2H_2O, and a total monomer dietary concentration (DC) of 92.8 µg/6 dm^2 (equivalent to 92.8 µg/kg food or drink) was used in the assessment.

52. An estimated daily intake (EDI) of 92.8 µg TMBPF-DGE monomers per person per day was determined by multiplying the dietary concentration by the total weight of food consumed by an individual per day (the conventional 1 kg food per person per day).

53. In the absence of any concerns for mammalian genotoxicity, developmental toxicity or bioaccumulation, the supplied documentation used the oral NOAEL of 100 mg/kg bw per day from the combined 28-days repeated dose toxicity study and an uncertainty factor of 1000 (100 for inter- and intra-species differences and a factor of 10 for subchronic to chronic extrapolation) to establish an acceptable daily intake (ADI) of 0.1 mg/kg. Therefore, for a 60 kg human the most conservative oral reference dose would be 6 mg/person per day.

54. For substances of low potential for mammalian carcinogenicity, the hazard quotient (HQ) approach can be used to quantify toxicological risk. The HQ is the ratio of estimated exposure to the ADI. A HQ of 1 or lower means adverse non-cancer effects are unlikely and thus use of the substance can be considered acceptable, for HQs greater than 1 the potential for adverse effects increases. The HQ for TMBPF-DGE and its monomers was 0.016.

55. The Committees agreed with the use of an uncertainty factor of 1000 to extrapolate from a 28-day study to lifetime exposure in humans. However, Members did not think that it was appropriate to establish a HBGV due to the lack of a long term/chronic toxicity study and other database deficiencies.

56. Comparing the estimated exposure with the NOAEL of 100 mg/kg bw per day for the 28-day study resulted in a margin of exposure (MOE) of at least 67,000. This

is well above the factor of 1000 (default of 100 x 10, as the NOAEL is from a subchronic study) considered appropriate to assess the level of concern from chronic exposure to the substance.

Toxicological Threshold of Concern

57. No previously established HBGV was available for TMBPF-DGE.

58. The threshold of toxicological concern (TTC) is a pragmatic, scientifically valid methodology to assess the acceptability of chronic exposure to substances of unknown toxicity found in food (EFSA, 2019). Considering the definitions for the three Cramer Classes, the COT concluded that TMBPF-DGE was Cramer Class III.

59. The estimated daily intake derived from the total monomer dietary concentration used for the migration of TMBPF-DGE was 92.8 µg/person, or 1.5 µg/kg bw and 1.2 µg/kg bw for a 60 kg and 78 kg person, respectively. The value is for the sum of all TMBPF-DGE derivatives detected in acetonitrile after 24 hours.

60. The estimated intake would be at or just below the TTC value of 1.5 µg kg/bw per day for a Cramer Class III compound.

Conclusions

61. The FCMJEG, COM and COT considered all available information at their respective meetings. It should be noted, that while testing was performed on TMBPF-DGE, as well as the epoxy resin, the following conclusions are on the safety of TMBPF-DGE only, and do not include evaluation of any of the other chemicals included in the manufacture of the epoxy resin or final product.

62. The migration of TMBPF-DGE and its derivatives was based on extraction in acetonitrile, which Members of the Committees agreed was the worst-case extraction and hence would be the worst-case migration of TMBPF-DGE. The anticipated migration of 1 mg/kg food is low and within the specific migration limit. The anticipated migration is also below the restriction of 9 mg/kg food applied to BADGE and bisphenol F diglycidyl ether (BFDGE), its closest comparators.

63. The Committees considered TMBPF-DGE to be genotoxic in vitro. However, while some uncertainties remain, specifically around the potential of TMBPF-DGE to induce polyploidy, the in vivo genotoxicity data were negative and provided a sufficient margin of safety. Overall, the Committees agreed that it is unlikely that there would be a risk to human health from any mutagenic effect of TMBPF-DGE.

64. Members concluded that the available, albeit screening-level, data on non-genotoxic endpoints did not indicate any reproductive or developmental effects at a concentration of 300 mg/kg or raise any other toxicological concerns at exposures of ≤ 100 mg/kg.

65. While not a requirement for the assessment, the endocrine data available for TMBPF-DGE epoxy resin were of good quality with the Committees concluding that there was no concern over endocrine effects of TMBPF-DGE at the expected exposure levels.

66. Members did not consider it appropriate to establish a HBGV due to the lack of a long term/chronic toxicity study and other database deficiencies.

67. Whilst uncertainties remain over the toxicological significance of the polyploidy induced by TMBPF-DGE and any potential long-term effects a chronic study may have revealed, the Committees concluded that there was sufficient information available to assess the safety of TMBPF-DGE under the proposed conditions of use.

68. When considering all available information, including a comparison of TMBPF-DGE with bisphenol A diglycidyl ether (BADGE), its closest comparator, the available data did not identify any safety concerns for the usage of TMBPF-DGE in can coatings. The MOE was at least 67,000, well above the value of 1000 considered to indicate a lack of any safety concern. In addition, the TTC approach provided re-assurance, given its in-built conservatism and supported the conclusion that the estimated exposure to TMBPF-DGE would be below any level of potential concern. Hence, the FCMJEG and COT did not see any scientific reason to apply restrictions to the proposed usage of TMBPF-DGE.

COT/FCMJEG
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