COT evaluations

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Safety of Titanium dioxide (E171) as a Food Additive

1.1 Food grade titanium dioxide (TiO2) was an authorised Food Additive (E171) in the EU, but from the 7th of August 2022, its use in food has been banned in light of the European Food Safety Authority's (EFSA's) conclusion that such use could no longer be considered as safe. It currently remains authorised in Great Britain. Food grade TiO2 comprises a mixture of micro- and nanosized (<100 nm) particles and is used in food as a colour (white pigment). Titanium dioxide is also widely used in cosmetics and medicines.

1.2 Titanium dioxide has been the subject of multiple safety evaluations including three recent evaluations by EFSA in 2016, 2019 and 2021.

1.3 In their most recent Opinion (2021), the EFSA Panel concluded that E171 could no longer be considered as safe for use as a food additive, due to uncertainties in some of the data, such as on genotoxicity (DNA damaging effects). Following this, in 2021 the COT published an interim position on titanium dioxide in which the Committee expressed its scientific concern about the basis of the EFSA conclusions. A detailed review has now been undertaken by the COT, which includes the conclusions on genotoxicity (DNA damaging effects) from the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM), to assess the safety of TiO2 as a food additive.

1.4 The COT has reviewed toxicological studies that have been conducted using any form of TiO2, including nanoparticles, but its conclusions are based primarily on those which used food grade TiO2 (E171), which predominantly consists of aggregates, of smaller primary particles, with a median particle size of 200 – 300 nm. The following endpoints were reviewed by the COT: the development of aberrant crypt foci (ACF) in the intestine (as a potential indicator of carcinogenicity), inflammation and immunotoxicity, reproductive and developmental toxicity and neurotoxicity. The COM reviewed the data on genotoxicity (damage to DNA which could ultimately lead to cancer) and reported their findings to the COT in May 2024.

1.5 The COT considered that the data from the relevant studies available indicated that TiO2 did not induce ACF, nor were there significant effects in studies that assessed inflammation and immunotoxicity, reproductive and developmental toxicity, and neurotoxicity. On balance, the Committee considered that a no observed adverse effect level (NOAEL) of 1,000 mg/kg bw per day, was robust.

1.6 Overall, the COM concluded that there was little evidence in the literature to suggest that food grade TiO2 (E171) caused induction of genotoxicity (DNA damaging effects), and that there was unlikely to be any health concern related to genotoxicity induction from use of TiO2 (E171) as a food additive. Following discussions of the COM report at their meeting in March 2024, the COT included the COM conclusions in their overall review of the evidence.

1.7 The COT concluded that 1,000 mg/kg bw per day was a robust Point of Departure (POD) on which to base a health-based guidance value (HBGV). This was the highest dose tested, so it is not known how much more TiO2 would have to be administered before effects were seen.

1.8 A standard uncertainty factor of 100 (10 for inter-species differences and 10 for inter-individual variability) was agreed by Members and applied to the POD which resulted in a HBGV (acceptable daily intake) of 10 mg/kg bw per day.

1.9 Titanium dioxide (E171) can be found in a number of food categories, and the exposures calculated and considered by the COT for infants, toddlers, children, adolescents, adults, and the elderly used food consumption data from UK surveys and maximum occurrence levels of titanium dioxide reported by EFSA (2021).

1.10 Estimated exposures for adults (18+) and the elderly are below the established HBGV. Although exposures for infants, toddlers, children and adolescents consuming a lot of TiO2-containing food are estimated to be 1.3 - to 2.6-fold higher than the HBGV, actual exposures are likely to be lower and in addition, the HBGV is likely to be conservative. Therefore, adverse health effects would not be expected.

1.11 The COT concludes that it is unlikely that there would be a risk to health from current UK dietary exposures of E171 TiO2.

1.12 The full COT statement can be found at: Safety of Titanium dioxide (E171) as a Food Additive.

Statement on the potential health effects of raspberry leaf tea in the maternal diet

1.13 The Scientific Advisory Committee on Nutrition (SACN) is reviewing the scientific evidence that bears on the Government's dietary recommendations for women of childbearing age. To help SACN in this, the COT was asked to review the risks of toxicity from certain chemicals and products in the maternal diet. This statement focuses on the possible risks from taking raspberry leaf tea, or extracts of raspberry leaf, in tablets or tinctures, during pregnancy.

1.14 Raspberry leaf, as tea, tablet or tincture, is most commonly taken during pregnancy as a dietary supplement in the belief that it stimulates and facilitates labour and shortens its duration. A recent study in Australia reported use by 38% of pregnant women, while a UK study in 2007-2008 reported use by approximately 24% of pregnant women. In addition to such preparations, several raspberry leaf products are registered as traditional herbal medicines in the UK. However, these are directed at non-pregnant women for the symptomatic relief of menstrual cramps. Some clinics offer enemas containing raspberry leaf, though it is not clear whether any are aimed at pregnant women.

1.15 A number of studies, starting in the 1940s, have investigated the effects of extracts of raspberry leaf on the uterus (womb) or other smooth muscle, either in intact animals or isolated from animals. The results of these studies were highly variable, with some showing smooth muscle contraction and others relaxation. This variability was likely due to factors such as differences in the components in the extracts and doses of the extracts tested, the type of smooth muscle tissue tested, pregnancy status of the animal, and whether the study was in an intact animal or on isolated uterus or other smooth muscle. The mechanism by which raspberry leaf could have the claimed effects on labour is also poorly understood, and it is unclear what the active components might be. A number of mechanisms have been suggested, but the evidence for these is limited and contradictory.

1.16 Limited data were available on the reproductive toxicity of raspberry leaf in laboratory animals, and only one study was identified that had evaluated it for short-term repeat-dose toxicity, conducted in mice. Another source of uncertainty was a lack of specific information on the absorption, distribution, metabolism and excretion of the constituents of raspberry leaf by the body following their consumption. However, some evidence indicated that raspberry leaf extracts are less toxic when given to mice orally than when injected intravenously. This

suggests that they have poor oral bioavailability; that is, that only small amounts of the toxic constituents reach the systemic circulation following ingestion.

1.17 Limited data were found on levels of contaminants, such as heavy metals, in raspberry leaf, and on levels of pesticide residues. However, the data available did not indicate any safety concerns.

1.18 The COT also took into account the available human data. These included two studies conducted in Australia. The first identified women who had given birth in hospital and who had taken raspberry leaf tea, tablets and/or tinctures during pregnancy, and compared them to matched women who had not taken raspberry leaf during pregnancy. No adverse effects were identified in the mothers or infants, or on the delivery, from consuming raspberry leaf. The second study, by the same group, was a double-blind, placebo-controlled trial, in which women were randomly assigned to receive raspberry leaf tablets or placebo tablets during pregnancy. No adverse effects were identified, with the possible exception of constipation, which was reported exclusively by 4 of the 96 women receiving raspberry leaf. However, the COT noted that estimates of UK consumption of raspberry leaf tea, or of raspberry leaf from tea, tinctures and capsules combined, which were based on data collected from online sources, were up to four or more times higher than the raspberry leaf dose tested in this trial.

1.19 In addition, the COT took into account data collected by the UK Teratology Information Service (UKTIS), a national service that collects pregnancy outcome data from women exposed to medicines and chemicals in pregnancy. There have been very few reports of adverse effects in pregnant women taking raspberry leaf or their children received by the UKTIS since its inception in 1983 to the present date, despite the reported high prevalence of use of raspberry leaf.

1.20 Overall, the COT concluded that the risk associated with raspberry leaf use during pregnancy was low but with high uncertainty due to the data limitations. The COT considered that poor oral bioavailability of the toxic constituents of raspberry leaf (based on indirect information) might also contribute to why it appears to have little adverse effect on human health. However, if raspberry leaf products that are modified to increase their bioavailability become available in the future, these may require a separate safety evaluation.

1.21 The full COT Statement can be found at: Statement on raspberry leaf tea.

Hepatotoxicity of green tea catechins

1.22 In 2017, following a series of reports of adverse effects on the liver following the consumption of green tea supplements, the European Commission requested the European Food Safety Authority (EFSA) to assess the available information on the safety of green tea catechins (principally - epigallocatechin-3-gallate (EGCG)) from all dietary sources including preparations such as food supplements and traditional infusions, with a focus on liver toxicity. At that time, and at the request of the Department of Health and Social Care (DHSC), who have the policy lead for food supplements in England, the FSA Chemical Risk Assessment Unit team reviewed the EFSA opinion informally and agreed with its conclusions.

1.23 Following a request to the Food Standards Agency from DHSC under the Nutrition, Labelling, Composition and Standards (NLCS) Common Framework, the COT have been asked to evaluate whether the conclusions of the 2018 EFSA opinion are still applicable (EFSA, 2018), in view of any new data that have become available since its adoption. Conclusions made by the Committee will help inform the next steps for risk management. The 2018 EFSA opinion itself and its evaluation by the COT, focus on green tea catechins and the associated cases of probably idiosyncratic hepatotoxicity, rather than being a safety assessment of either green tea catechins or green tea infusions and extracts more generally.

1.24 The COT concluded that EFSA's conclusions were still applicable and that 800 mg/day EGCG was probably safe. However, it is possible that some sensitive individuals will experience an idiosyncratic reaction below this dose.

1.25 The technical statement and lay summary have been published and are available on the COT website and through the following DOI link: https://doi.org/10.46756/sci.fsa.wii944.

Assessment of Bisphenol A (BPA)

1.26 Following extensive reviews and discussions of the scientific evidence of the new European Food Safety Authority (EFSA) tolerable daily intake (TDI) for bisphenol A (BPA), and the subsequent assessment by the German Federal Institute for Risk Assessment (BfR) in 2023, the COT adopted the tolerable daily intake (TDI) of 0.2 µg/kg bw per day established by the BfR.

1.27 The Committee noted that the scientific issues raised by the BfR aligned with the concerns and comments highlighted by the COT during their discussions and the public consultation held by EFSA.

1.28 The use of a male reproductive endpoint, i.e. sperm count and mobility, by the BfR was consistent with the critical endpoint used in previous COT assessments. While the COT agreed that the BfR had added a significant degree of conservatism in their establishment of the TDI, they could not identify any endpoint that would be more suitable and concluded that the overall assessment by the BfR and endpoint applied, and approach taken was reasonable.

1.29 In line with EFSA and the BfR, the Committee highlighted that the most recent exposure data available predates the 2015 EFSA opinion. To be able to undertake a full risk assessment, the COT will require up to date exposure data, which will enable the Committee to fully assess realistic exposures in, and potential risks to, the UK population.

1.30 The position paper was published in May 2024 and can be viewed using this link: Position paper on bisphenol A | Committee on Toxicity.

1.31 The Committee will be publishing a supplementary statement in 2025, providing more detail on their discussions of the EFSA opinion and BfR assessment, their evaluation of the evidence base, and deliberations to adopt the TDI established by the BfR.

Updated position paper on Bamboo Bio-Composites in Food Contact Materials

1.32 Risk assessment advice on biobased food contact materials (BBFCMs) has been increasingly requested from the Food Standards Agency (FSA), hence it was considered timely for the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to review the available toxicological information on BBFCMs (COT, 2021) including bamboo bio-composites.

1.33 In 2019, the European Commission (EC) asked the European Food Safety Authority (EFSA) to assess whether the authorisation of untreated wood flour and fibres (FCM no. 96) as an additive in plastic food contact materials was still in accordance with EC Regulation 1935/2004, and also to consider whether bamboo could be considered under the scope of this authorisation. Following EFSA

conclusion that wood and bamboo should be considered distinct, and each material regarded on a case-by case basis, the EC recommended that Member States should take stringent action on bamboo composite FCMs and set out a coordinated control plan. In addition, the food safety authorities of Belgium, Luxembourg and the Netherlands (Benelux) published a joint letter calling for the market withdrawal of bamboo-melamine plastics. The FSA is aware of the stance by the EC and of the individual Member States and is considering an appropriate course of action based on scientific evidence.

1.34 In December 2020, reports to the FSA in relation to bamboo composite FCMs were predominantly related to misleading labelling on packaging and/or their advertisement, as well as incidences of formaldehyde/melamine migration levels exceeding legal limits. In 2021, and due to the EU's conclusion, that bamboo is an unauthorised additive within plastic FCMs, reports received by the FSA had predominantly been of non-compliance of plastic-bamboo FCMs in the European market. This included the advertisement of products from UK businesses on EU facing markets. Hence, the COT undertook a more detailed review of the potential health risks of bamboo composites in Food Contact Materials (FCMs).

1.35 The COT assessed the reports by the German Federal Institute for Risk Assessment (BfR) and the Netherlands Food and Consumer Product Safety Authority (NVWA) and noted that the BfR applied their own tolerable daily intake (TDI) of 0.6 mg/kg/day for formaldehyde whereas the NVWA and EFSA used a lower TDI of 0.15 mg/kg/day.

1.36 Overall, the COT concluded that the exposure assessments were conservative but not necessarily worst-case. It was agreed that although the NVWA and BfR opinions took slightly different approaches, in general the same conclusions were reached. Based on the assessment of the BfR and NVWA reports the Committee concluded that the migration of formaldehyde and melamine from bamboo composite cups was a potential concern to human health.

1.37 To assist the COT with their assessment the FSA launched a call for evidence in 2023 to obtain further information from industry, consumers, or interested parties on the safety and stability of plastic contact materials and articles containing bamboo and other plant-based material. In March 2024, the COT assessed the information submitted to the FSA in response to the call for evidence as well as an additional report (EU-ChinaSafe, 2022).

1.38 Based on the considerations of the new evidence submitted to the FSA and the currently available data, the COT agreed that there was still insufficient exposure data on which to perform a complete risk assessment. Concerns remained regarding the migration of formaldehyde and melamine from these FCMs, while the actual composition of these products remained uncertain.

1.39 The updated position paper can be viewed using this link: TOX-2021-59 Interim position paper on bamboo composites in food contact materials.

Joint statement on the safety assessment of Tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE)

1.40 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.

1.41 As the European Food Safety Authority (EFSA) had not carried out an assessment 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).

1.42 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.

1.43 All information provided to the FSA on TMBPF-DGE has been 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.

1.44 TMBPF-DGE is a mixture derived from the reaction of tetramethyl bisphenol F (TMBPF) with epichlorohydrin. TMBPF-DGE is then 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 (including beverages). It should be noted, that while testing was performed on TMBPF-DGE, as well as the epoxy resin, the assessment is on the safety of TMBPF-DGE only and does not include evaluation of any of the other chemicals included in the manufacture of the epoxy resin or final product.

1.45 TMBPF-DGE contains epoxy (glycidyl) groups which are intended to be reactive. TMBPF-DGE derived epoxy groups may remain in the resin however after polymerisation they are incorporated into the finished (cured) polymer resin hence no availability for interaction with food substances is anticipated.

1.46 The migration of TMBPF-DGE and its derivatives was based on extraction in acetonitrile, which the Committees agreed was the worst-case extraction and hence would represent the worst-case migration of TMBPF-DGE. The anticipated migration was within the specific migration limit and also below the restriction to bisphenol A diglycidyl ether (BADGE) and Bisphenol F diglycidyl ether (BFDGE), its closest comparators.

1.47 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.

1.48 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.

1.49 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.

1.50 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.

1.51 When considering all available information, including a comparison of TMBPF-DGE with 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.

1.52 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 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.

1.53 The joint statement was published in 2024 and can be viewed using this link: Summary and Introduction | Committee on Toxicity.

Aircraft cabin air

1.54 The COT was asked to consider the question: “Is there evidence of exposure to chemical contaminants, in cabin air that could have long-term health impacts, either from acute exposures or due to long-term low level exposures including mixtures, e.g., of volatile organic compounds?”. This follows a COT statement in 2007 addressing aircraft cabin air, relating to organophosphate compounds, the cabin air environment, ill-health in aircraft crews and the possible relationship to smoke or fume events (COT, 2007) and subsequently a position statement following research on aircraft cabin environment (COT, 2013).

1.55 The objective of the present review was to investigate whether specific chemicals commonly identified in aircraft cabin air could potentially cause ill-health in aircrew. This review did not look for other potential causes of aircrew ill-health (these were considered in the 2007 review).

1.56 For the present review the COT considered a number of papers on organophosphates, volatile organic compounds, carbon monoxide and carbon dioxide.

1.57 Most of the published information on these chemicals in aircraft cabin air related to background levels during normal flight operation. There continued to be only very limited information on levels following smoke or fume events, with little additional data since COT’s previous work in 2007 and 2013. Smoke or fume events are when abnormal odours, smoke, haze or fumes occur in the aircraft

cabin, which may come from various internal or external sources.

1.58 The COT considered the potential risk to health from organophosphate exposure in aircraft cabin air (TOX/2022/40). Two studies investigated health effects in aircrew. The COT considered there were shortcomings with both studies, in particular neither study reported the levels of organophosphate exposure the crew had experienced. However, the COT agreed with the authors' conclusions that the data did not indicate any association between impact on mental ability and organophosphate exposures.

1.59 One paper carried out a risk assessment for a specific organophosphate, tri-ortho-cresyl phosphate, commonly used in aviation lubricants. Levels of exposure to this organophosphate were substantially below those at which a risk of adverse effects on health might arise.

1.60 The Committee concluded that it was unlikely that exposure to organophosphates at the low levels identified in aircraft cabin air would have adverse effects on aircrew.

1.61 For volatile organic compounds, levels in aircraft were compared with levels in other modes of transport (TOX/2022/46) or other work environments (TOX/2022/55) in the UK and EU. If the highest average levels of an individual compound in aircraft were above all the highest average levels in other environments in which that individual compound was measured, the COT carried out a specific risk assessment for that chemical.

1.62 The reported levels of six volatile organic compounds in aircraft were above the levels in other UK and EU modes of transport or work environments (TOX/2023/15). However, the concentrations were all lower than relevant guidelines and standards, indicating that no risk to health is anticipated at these levels. Mixtures of volatile organic compounds were considered using a hazard index approach. This compares the level of each chemical with the level below which there would not be a risk to health and adds these ratios together. In considering the volatile organic compounds in aircraft cabin air, the result of this hazard index approach indicated that no effects, including mixture effects, are anticipated.

1.63 Levels of carbon monoxide and carbon dioxide in UK and EU-operated aircraft were collated and compared with various standards as well as levels that cause discernible symptoms (TOX/2022/65 and TOX/2023/14). The Committee considered these data and concluded that levels of carbon monoxide and carbon

dioxide reported in aircraft are unlikely to be associated with any short- or long-term adverse health effects.

1.64 Overall, the COT concluded that the levels of the chemical contaminants reviewed (organophosphates, volatile organic compounds including as mixtures, carbon monoxide and carbon dioxide) in aircraft cabin air, at the concentrations reported, are unlikely to cause adverse health effects in aircrew after being exposed for long or short time periods. However, there is still limited information about the levels of chemicals in cabin air following smoke or fume events.

1.65 The full COT statement can be found at: Statement on Aircraft Cabin Air Quality | Committee on Toxicity.