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

Update Statement on the Toxicology of Terephthalic Acid

Background

1. Terephthalic acid (TPA; Figure 1) is used as a starting material in the manufacture of polyethylene terephthalate (PET). PET may be used to coat the internal surface and welded joints (side stripes) of food cans. PET can also be used to manufacture beverage bottles.

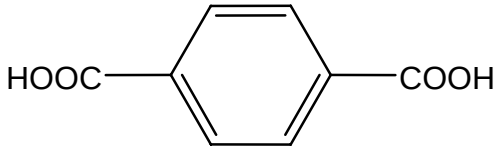

Figure 1. Terephthalic acid

2. In research on potential for contamination of food, TPA was found to migrate from can coatings into food at levels between the limit of detection (0.2 mg/kg food) and limit of quantification (0.7 mg/kg food) of the assay employed[1] Subsequently, TPA was included in a Food Standards Agency (FSA) funded survey of plastic materials and articles in contact with food, which examined compliance with statutory limits on composition and migration[2]. In this survey, fifty foods packaged in PET were tested, with no measurable migration of TPA into the food simulant[a].

3. In law, migration from can coatings is subject to the general requirement that applies to all food contact materials and is laid down by Article 3 of Regulation (EC) 1935/2004. This requires that food contact materials and articles should not transfer their constituents to foodstuffs in quantities that could endanger human health or affect the nature or quality of the food. In addition, migration of TPA is specifically controlled where it is used in food contact plastics. Commission Directive 2002/72/EC lays down a specific migration limit (SML) for TPA of 7.5

[a] Food simulants are standard test liquids, specified in Directive 85/572/EEC, which are used to simulate real foods in migration studies. The specified simulants, to be used depending on the particular food types being tested, are: distilled water; 3 % acetic acid (w/v in aqueous solution); 15 % ethanol (v/v in aqueous solution); and rectified olive oil. Where there are technical difficulties using rectified olive oil, substitute fatty food simulants such as sunflower oil or synthetic triglycerides may be used.

mg/kg food or food simulant. This is enacted in England by The Plastic Material and Articles in Contact with Food (England) (No.2) Regulations 2006, with parallel legislation in Scotland, Wales and Northern Ireland.

4. In 1986, the Scientific Committee on Food (SCF) reviewed the toxicology of TPA and established a temporary tolerable daily intake (t-TDI) of 0.125 mg/kg bw/day[3]. Although details of the derivation are not available, it was presumably based on a 90-day oral feeding study in male and female Wistar and CD rats, with application of a 500-fold uncertainty factor to the no observed adverse effect level (NOAEL) of 0.125% TPA in the diet, equivalent to 62.5 mg/kg bw/day (calculated assuming adult rats consume 20 g of food per day with an average body weight of 400 g). Reduced body weight gain was reported at levels of 0.5, 2 and 5% TPA in the diet in the 90-day oral feeding study. In a separate reproductive toxicity study, formation of renal and bladder calculi was observed at postnatal day 51 in Wistar and CD rats consuming 5% TPA in the diet. The t-TDI was classed as temporary pending the submission of the full report of this study. However, the SCF does not appear to have revisited the risk assessment and re-evaluation of terephthalic acid is included in the current work programme of the European Food Safety Authority (EFSA).

Previous COT Evaluations

5. In October 2000, the COT considered the possible health effects of TPA in the context of the survey on the migration from can coatings into food[1]. Dietary intakes of TPA from canned foods were estimated for high level (97.5th percentile) consumers. These estimates ranged from 2.5 µg/kg bw/day for adult consumers, to 7.4 µg/kg bw/day for infants. The COT concluded that these exposures were not of concern for public health on the basis of the then available information. However, although the submitted data did not indicate that TPA can modulate the endocrine system, the studies were inadequate to exclude the possibility. This was a concern because of structural similarities to phthalate esters that are reported to have endocrine-disrupting potential. It was therefore recommended that a suitable study be conducted to determine whether TPA has endocrine-disruptor activity. Furthermore, in view of the occurrence of urinary bladder tumours in Fischer F344 rats fed the highest dietary concentration of TPA (2% in the diet) in a 2-year carcinogenicity study, the COT recommended that an opinion be sought from the COM on the potential *in vivo* genotoxicity of the compound[4] in order to gain insights into the likely mechanism of tumour formation.

<u>Reproductive Toxicity</u>

6. In June 2003, a manufacturer submitted the report of a full multi-generation reproductive toxicity study, which concluded that dietary administration of up to 20 g/kg diet TPA for two successive generations did not result in any alterations in reproductive performance.

7. In 2003, Members noted that the bodyweights of the pups in this study were comparable at birth, except for the F_2 generation, where a lower weight was associated with larger litter size. Observed differences in pup bodyweights at later ages were thought likely to result from a direct effect of the TPA on the pups, and were not considered to be developmental effects. Observed changes in developmental endpoints were considered likely to result, in turn, from the reduced bodyweight and size of the pups. It was also noted that the effect of TPA on anogenital distance (AGD) was larger than the effect on bodyweight, although there was no clear dose-response relationship.

8. Overall, Members were satisfied that the information provided in the report was sufficient to demonstrate that terephthalic acid did not have endocrine-disrupting effects at the highest dose tested in this study, resulting from administration of TPA at 20 g/kg diet. Subsequently, Members have noted emerging evidence that this type of study might not be sufficiently sensitive to anti-androgenic activity. In 2003, since histopathological changes in the urinary bladder and the kidney were reported at 20 g/kg, Members considered that further histopathological examination was required.

Histopathology of the kidney and urinary bladder

9. Members noted that reductions in kidney weights occurred at all doses of TPA, making the 1g/kg diet dose level (equivalent to 100 mg/kg bw/day, calculated assuming young rats consume 10 g of food per day with an average body weight of 100 g) the lowest observed effect level (LOEL) for the effect on kidney weight. Histopathological changes in the urinary bladder and the kidney were reported at the high dose (20 g/kg diet), but these organs had not been examined in the mid- and low-dose groups (1 and 5 g/kg diet). Therefore, the Committee considered it important to receive further information about the effects observed in the kidneys and the urinary bladder.

10. In March 2005, a report describing further histopathological examinations of the kidneys and urinary bladder of animals in the TPA multi-generation study was submitted to the COT. This was accompanied by an expert report discussing the histopathology of the kidneys of animals in this study.

11. A variety of changes were observed in the urinary bladder of rats of both sexes receiving 20 g/kg diet TPA. These changes comprised transitional epithelial hyperplasia, cystitis, inflammatory or mononuclear cell infiltration and haemorrhage. The incidence of observed changes was higher in the F_1 generation than in F_0 animals possibly reflecting the longer period of exposure of the former. The author considered that these changes were related to treatment and indicated an irritant effect of the compound on the bladder mucosa at this dose level. No changes were observed in the bladders of animals receiving 1 or 5 g/kg diet TPA or in controls.

12. Minimal or slight renal papillary necrosis was observed in the kidneys of a few males (2/10 F_0 and 2/11 F_1) receiving 20 g/kg diet TPA but not in any of the control or lower dose group males. Similar changes were observed in 3/10 F_0 females receiving 20 g/kg diet. However minimal papillary necrosis was also observed in 1/10 control F_0 females and 1/10 F_0 females receiving 1 g/kg diet TPA. Necrosis, classified as slight, was confined to animals (1 F_0 male and 1 F_0 female) receiving 20 g/kg diet TPA. Although the increase in incidence and severity versus controls was small, the author of the report considered it likely that this was related to treatment with TPA. No other gross or microscopic changes were detected in adults or pups. The NOAEL for pathological changes in this study was 5 g/kg diet TPA.

13. The submitted expert report also considered the observed toxicity of TPA to the urinary system of the rat in a combined 90-day and one-generation reproductive study in Wistar and CD (Sprague Dawley) rats, a two-generation reproductive toxicity study in Alpk:APfSD (Wistar-derived) rats and a chronic/oncogenicity study in Fischer 344 rats. A number of treatment-related histopathological findings were reported in the urinary system but no consistent pattern of renal toxicity was observed across the available studies. In addition there was little evidence to suggest differing susceptibility amongst rat strains with regard to renal toxicity. The author of the report considered that potentially adverse histopathological findings in the two-generation reproduction study were confined to an increase in incidence and severity of papillary necrosis in the F_0 and F_1 parents, which had a clear NOAEL.

14. The physiological response of the rat kidney to TPA has been characterised in multiple studies and includes urinary acidification with increased urinary excretion of calcium and phosphorus. Consistent treatment-related findings in these studies were confined to the bladder and included chronic inflammatory, hyperplastic and neoplastic changes; these occurred both in the presence and absence of calculi. The pattern of treatment-related bladder findings in Alderley Park Wistar-derived rats was consistent with those observed in the bladder of other rat strains. The report noted that kidney weight reduction was observed in F_0 adult rats which had not been exposed *in utero*; without associated adverse pathological changes in the kidney, or urinary system as a whole; and at doses that did not affect the growth and development of treated rats.

15. Members were satisfied that the additional histopathological data indicated a clear no observed adverse effect level (NOAEL) for histopathological changes in the urinary bladder and kidney (renal papillary necrosis) corresponding to administration of TPA at 5 g/kg in the diet in the multi-generation study. Statistically significantly decreased renal weights (adjusted for bodyweight) were present in all generations including the parental generation. However, given that there was no associated histopathology or effect on renal function, it was not clear whether this effect should be considered adverse. It was also noted that

this effect was not observed in a chronic toxicity study using a different rat strain.

16. It was agreed that the relevance of the effect should be considered by applying internationally agreed criteria from the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) for distinguishing between adverse and adaptive effects[5]. This would provide a clear description of the rationale for the Committee's conclusions.

Application of ECETOC criteria for distinguishing between adverse and adaptive effects

17. Using this approach, effects are generally considered less likely to be adverse if: there is no alteration in the general function of the organism or organ; it is considered an adaptive response; and if the effect is not a known precursor of an adverse effect. Other considerations in reaching conclusions could include a lack of histopathology associated with an effect and reversibility of the effect if a recovery period was used in the experimental design.

18. As the kidney weight reductions occurred in the F_0 generation, as well as the offspring, this effect was not considered to be specific to development of the kidney. There were no treatment-related findings in the kidneys of F344 rats in a chronic/oncogenicity study. Other 90-day studies carried out using Wistar and Sprague Dawley rats did not find treatment-related effects on kidney weight.

19. The consultant veterinary pathologist reviewing the study for the sponsor considered the kidney weight reduction in the Alderley Park Wistar rats most likely to represent a colony-specific physiological adaptation to exposure to terephthalic acid.

20. The NOAEL from the multi-generation study was therefore the dose resulting from administration of TPA at 5 g/kg in the diet. This was in the region of 425 – 1200 mg/kg bw/day, depending on food consumption of the different treatment groups.

COM Evaluation

21. In November 2001, the COM evaluated a limited package *of* mutagenicity data. This included *in vitro* bacterial and mammalian mutagenicity assays that, although finding TPA to be negative, were either poorly reported or had inadequate protocols; and a negative *in vivo* mouse micronucleus assay.

22. The COM was provided with additional data in 2006. Although there was some concern over results of the *in vitro* mammalian cytogenetics test, this did not meet the criteria for a positive result. An additional *in vivo* unscheduled DNA synthesis assay (UDS) was also supplied which, together with the mouse micronucleus assay, were considered sufficient to indicate that TPA is not an *in vivo* mutagen. Therefore, the available

evidence was considered to support a non-genotoxic mechanism for the bladder tumours seen in the rat carcinogenicity study[6].

Conclusions

23. We note the conclusions of the COM that terephthalic acid lacks *in vivo* genotoxicity, which supports there being a non-genotoxic mechanism of action for bladder tumour formation.

24. We are satisfied that the submitted reproductive toxicity study demonstrates that terephthalic acid is not an endocrine-disruptor.

25. The decreased kidney weights in the multi-generation study probably constitute an adaptive rather than adverse effect. Therefore, this is unlikely to be a cause for concern with regard to human exposure to teraphthalic acid.

26. Histopathological changes in the kidney represent the most sensitive toxicological endpoint, allowing the identification of a NOAEL at a dose level equivalent to 425 mg/kg bw/day. High level (97.5th percentile) consumer dietary intakes of TPA from canned foods were estimated from the FSA survey[1]. These ranged from 2.5 µg/kg bw/day for adult consumers, to 7.4 µg/kg bw/day for infants; indicating margins of exposure of 170,000 and 57,000 for adults and infants respectively.

27. Therefore, in line with our previous statement[4], we do not consider the concentration of TPA found to migrate from food can coatings in the FSA funded study to be of concern for public health. The new data evaluated do not indicate a need to lower the temporary TDI of 0.125 mg/kg bw/day, proposed by the SCF and scheduled for re-evaluation by the EFSA expert panel on food contact materials, enzymes, flavourings and processing aids.

References

[1] Food Surveillance Information Sheet No. 7/00. (October 2000). Chemical Migration From Can Coatings into Food - Terephthalic and Isophthalic Acids. http://www.food.gov.uk/science/surveillance/fsis2000/7phthal

[2] Food Surveillance Information Sheet No. 43/03. (October 2001). Chemicals used in plastic materials and articles in contact with food. http://www.food.gov.uk/multimedia/pdfs/fsis4303.pdf

[3] Report of the Scientific Committee for Food on certain monomers and other starting substances to be used in the manufacture of plastic materials and articles intended to come into contact with food (1982) Reports of the Scientific Committee for Food, Seventeenth Series, http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_17.pdf

[4] COT Statement on terephthalic and isophthalic acids from can coatings (COT/2000/08) http://www.food.gov.uk/multimedia/pdfs/cotacids.pdf

[5] European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical report No 85; Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies

[6] COM Statement on the Mutagenicity of Terephthalic Acid (COM/07/S6) http://www.advisorybodies.doh.gov.uk/pdfs/tpa07.pdf