Outcome of the toxicological evaluation on Cyclo-di(bisphenol-A-monoglycidyl ether) [CAS: 20583-87-3] and calculation of a self-derived Tolerable Daily Intake level (sTDI) carried out by the Rigid Metal Packaging Supply Chain[1]

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Epoxy resins based upon BADGE have been used extensively as a major film forming component for can coatings. In the past concern was raised by some EU Member States about the presence of cyclodiBADGE (CDB) being found in in extracts from these can coatings. CDB is a is a minor by product formed during the manufacturing of epoxy resin based coatings applied to the food contact surfaces of food and beverage cans and CDB is classified as a NIAS (Non-Intentionally Added Substance). CDB has been found in some cases in various canned foodstuffs at varying concentrations. To date no toxicological data was available on this substance leading to concerns from some over the contaminant levels identified in canned food products.

As the reported levels exceeded the thresholds established under the Threshold of Toxicological Concern methodology, a concern for potential adverse effects could not be ruled out. About 7 years ago the Joint Industry Group (epoxy manufacturers, coatings manufacturers and can makers) decided to carry out a toxicological testing programme to identify any toxicological concerns with CdB and ally any concerns about its toxicity. This paper summarises the results from a peer reviewed publication (https://www.sciencedirect.com/science/article/pii/S0278691526000268?ref=pdf_download&fr=RR-2&rr=9d040c788e301327).

As CdB is a contaminant and not commercially available sufficient quantities of radio-labelled CDB were synthesized specifically for testing. The tests were carried out to OECD guidelines as follows:

1. In vitro mutagenicity test in bacteria (Ames), OECD TG 471
2. In vitro micronucleaus assay, OECD TG 487
3. Sub-chronic (90d) study in rats via dietary administration, OECD TG 408
4. Toxicokinetics, OECD TG 417

CdB showed no evidence of mutagenic effects in bacteria or a clastogenic potential in human lymphocytes in vitro with and without metabolic activation. Dietary administration of 0, 1500, 5000, 15000 ppm CdB to rats for 90days resulted in no substance specific adverse effects at all dose levels tested. The NOAEL was established as at least 15,000ppm in the diet corresponding to 1139 mg/kg bw/day for males and 1366 mg/kg bw/day for females. Toxicokinetic investigations demonstrated that after oral administration of C^{14} radio labelled CdB to rats, the test substance was mostly excreted via feces within 48 hours and to a minor extent via bile and urine suggesting limited absorption in the intestinal tract. Overall recovery in feces, bile and urine does not indicate a relevant bioaccumulation potential. Based on the resulting of the testing CdB does not raise any significant toxicological concerns. Industry is preparing a manuscript for publication which will include full details of the toxicity studies.

As briefly described above, available toxicological data for CdB do not indicate any relevant adverse effect. Therefore, using the lowest NOAEL of 1139 mg/kg bw/day for male rats as starting point is considered appropriate for calculating a sTDI. According to the principles and by using uncertainty

[1] Supply chain made of the resin, the coating and the rigid metal packaging manufacturers

factors as laid down by EFSA[2] an uncertainty factor of 200 has been derived. Applying this uncertainty factor to the NOAEL results in a sTDI for CdB of 5.7mg/kg bw/day. It must be noted that this is a pure health-based value. Other threshold values may apply depending on applicable regulations. This value is considered conservative given it is derived from the highest dose used in the study and where no adverse effects were observed.

This exercise illustrates the issues surrounding a comprehensive toxicological assessment of any NIAS. The exercise involved different parties in the supply chain (listed above) and was resource intensive. Some of the issues encountered are summarised below:

- Supply chain collaboration.
- No clear regulatory guidance on testing approach.
- Finding a laboratory able to produce sufficient test material to carry out the required tox testing.
- Producing radiolabelled material.
- Significant costs for manufacturing test substance and radiolabelling.
- 114 animals used.
- External costs were ~700,000 Euros.

As most coatings and Food Contact Materials contain a number of NIAS at different concentrations, this exercise illustrates the difficulties associated with testing all of them particularly when the NIAS are not commercially available. Thus, it is concluded that toxicological testing is not feasible for all NIAS and a different approach to risk assessing them is required.

[2] EFSA Scientific Committee; Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579. [32 pp.] doi:10.2903/j.efsa.2012.2579.