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Derivation of safe health-based exposure limits for potential consumer exposure to styrene migrating into food from food containers

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ABSTRACT

Residual styrene present in polystyrene food packaging may migrate into food at low levels. To assure safe use, safe exposure levels are derived for consumers potentially exposed via food using No/Low Adverse Effect Levels from animal and human studies and assessment factors proposed by European organisations (EFSA, ECHA, ECETOC). Ototoxicity and developmental toxicity in rats and human ototoxicity and effects on colour discrimination have been identified as the most relevant toxicological properties for styrene health assessments. Safe exposure levels derived from animal studies with assessment factors of EFSA and ECHA were expectedly much lower than those using the ECETOC approach. Comparable safe exposure levels were obtained from human data with all sets of assessment factors while ototoxicity in rats led to major differences. The safe exposure levels finally selected based on criteria of science and health protection converged to the range of 90–120 mg/person/d. Assuming a consumption of 1 kg food/d for an adult, this translates to 90 mg styrene migration into 1 kg food as safe for consumers. This assessment supports a health based Specific Migration Limit of 90 ppm, a value somewhat higher than the current overall migration limit of 60 ppm in the European Union.

1. Introduction

Polystyrene (PS) is extensively used as food packaging material mainly in the form of GPPS (general purpose polystyrene), HIPS (high impact polystyrene) and EPS (expanded polystyrene) or in copolymerisation with other monomers, especially acrylonitrile and butadiene. Due to the production process styrene monomer (S) is found in residual amounts in such polymer food containers, due either from unreacted S in the starting polymer before converting or from thermal depolymerisation during the converting process. In current S-based polymer grades, the amount of the monomers may reach about 500 mg S/kg PS (O'Brian, 2001).

In the present EU regulation for plastic materials and articles intended to come into contact with food (EU, 2011) S is listed without any restriction. Especially no Specific Migration Limit (SML) is defined; consequently the overall migration limit of 60 mg/kg food would apply. In 2003, WHO (2003) published a Tolerable Daily Intake (TDI) of 7.7 μg/kg bw/d, corresponding to 0.46 mg/person/d (based on 60 kg body weight). This latter TDI was based upon reduced body weight at 250 ppm in female rats in a 2-year drinking water study (Beliles et al., 1985) and derived by dividing the

Abbreviations: AF, assessment factor; bw, body weight; DNEL, Derived No Effect Level; ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals; ECHA, European Chemicals Agency; EFSA, European Food Safety Authority; EH, epoxide hydrolase; EPS, expanded polystyrene; GPPS, general purpose polystyrene; HED, human equivalent dose; HIPS, high impact polystyrene; JECFA, Joint FAO/WHO Expert Committee on Food Additives; LOAEL, Low Adverse Effect Level; LWAE, lifetime weighted average exposure; MA, mandelic acid; MAK, Maximale Arbeitsplatz Konzentration; NOAEL, No Adverse Effect Level; PGA, phenylglyoxylic acid; PS, polystyrene; RAC, RISK Assessment Committee of ECHA; RAR, Risk Assessment Report of the EU; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; RfD, Reference Dose; S, styrene; SEL, safe exposure level; SML, Specific Migration Limit; SO, styrene-7,8-oxide; SSC, Styrenics Steering Committee; TDI, Tolerable Daily Intake; TWA, time weighted average exposure; UK, United Kingdom; US FDA, Food and Drug Administration of the U.S. Department of Health and Human Services; WHO, World Health Organisation.

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NOAEL (125 ppm/7.7 mg/kg bw/d for males) by 1000. Health Canada (1993) and RIVM (2001) derived a TDI of 120 μg/kg bw/d based on the same NOAEL (125 ppm/12 mg/kg bw/d for females) but using an AF of 100. The US EPA (1990) derived an oral Reference Dose (RfD) of 200 μg/kg bw/d based on effects observed on haematology and liver in the dog at exposure concentrations higher than 200 mg/kg bw/d (oral intubation) in a 19 months study (Quast et al., 1979). An AF of 1000 was applied.

With the advent of the REACH regulation in Europe a procedure has been prescribed to establish Derived No Effect Levels (DNELs) for long-term exposure of the general population. Although DNELs are not intended to specifically address direct consumer ingestion these may provide a useful approach for the safety assessment of food contaminants. A DNEL (long term – oral route – general population) of 2.1 mg/kg bw/d was proposed for S (IUCLID, 2013). The calculation of DNELs is based on toxicity benchmarks, usually the No/Low Observed Adverse Effect Levels (NOAEL/LOAEL) found in experimental animals or epidemiological studies and the application of assessment factors (AFs).

There is a broad, albeit very low exposure of consumers to S via food packaging materials and some recent exposure estimates are reported. Safe exposure levels (SEL) are derived for consumers exposed to S via food. The toxicological endpoints that are nowadays considered as most relevant are taken into consideration, namely ototoxicity and colour vision disturbance in humans as well as postnatal developmental effects in rats. Especially the database for ototoxicity is robust in experimental animals and humans and concordant under qualitative and even quantitative aspects. Division of the NOAELs/LOAELs for these toxicity benchmarks by appropriate AFs leads to different SELs. This paper concentrates on AFs recently proposed by EFSA (2012), ECHA (2012) and ECETOC (2010) and therefore the results primarily relate to the European regulatory environment. The SELs will then allow defining a Specific Migration Limit (SML) for the migration of S into food. Since only toxicity data are taken into consideration this SML is solely based on health effects.

2. General considerations

2.1. Potential consumer exposure to styrene

The SELs and the SML finally arrived at in this paper should be put into context with actual data for potential consumer exposure via migration of S from PS food containers. Exposures have been measured or estimated by methods of different complexity and some more recent examples are given below:

1. *Use of food simulants under standardised conditions*: GPPS, HIPS and EPS were extracted with food simulants prescribed by European Directives (EC, 1997; EU, 2011), namely 3% acetic acid, 10% aqueous ethanol and olive oil for 2 h at 70 °C or 10 days at 40 °C (GPPS, HIPS) or 10 days at 5 °C (EPS), representing most closely the conditions of use for these polymers. The PS surface to food ratio was 6 dm^2/1 kg food equating the EU "standard cube" (1 kg food packaged in 6 dm^2 plastics packaging material). For GPPS and HIPS migration of S into 3% acetic acid or 10% ethanol was generally below 100 μg/kg, but reached 75–590 μg/kg in olive oil after 10 days at 40 °C. With EPS extracted for 2 h/70 °C somewhat higher concentrations were found (up to 340 μg/kg in olive oil), but clearly lower concentrations at 10 d/5 °C (up to 40 μg/kg in sunflower oil) (O'Brian, 2001).
2. *Food surveillance*: In 5 sets of a total diet study covering 100 categories of food (UK MAFF, 1999) S was detected at low levels of up to 14 μg/kg. Using consumption data from the National Food Survey the dietary exposure of consumer was estimated to be 0.03–0.05 μg/kg bw/d (1.8–3 μg/person/d). In a previous study (UK MAFF, 1994) covering 248 food samples packed in a variety of pack types the concentrations of S were generally in the range of <1–60 μg/kg with the exception of a "low fat" table spread (97 μg/kg) and milk and cream products sold as small portions (~10 g) for tea and coffee (23–230 μg/kg). In this latter case the high surface to volume ratio and the high fat content explain these higher concentrations. Subsequently 22 samples of such "coffee creamers" were specifically studied and relatively high concentrations of S were verified with a range of 13–316 μg/l (Offen et al., 1995).
3. *Compilation of data*: Tang et al. (2000) assessed human exposure to S on the basis of literature data. The average consumption profile of the general German population was utilised under the assumption that milk, milk products, fat and oil were all packed in PS materials. The daily S intake was estimated to reach 2–12 μg/person/d. A comparable estimate (9 μg/person/d) was obtained by Lickly et al. (1995) for people in the United States based on a consumption of 3 kg food/d. A probabilistic approach was used by Holmes et al. (2005) to calculate a median exposure for adults of 0.039 μg/kg bw/d (~2.4 μg/person/d). Vitrac and Leblanc (2007) used a probabilistic method to estimate S exposure via consumption of yogurt, a food item often packed in PS. They assumed an average S concentration for the food containers of 500 mg/kg and calculated for the daily uptake a 50th percentile of 12 μg/person/d.

To estimate the exposure of children (5–12 years) to S from food containers Duffey and Gibney (2007) used the type and amount of food consumed by children from the Irish National Children's Food Survey, including the type of packaging for these foods. A food was assumed to contain S if it was packaged in a material that might release the monomer. Migration values were taken from the literature and exposure estimates used either the 90th percentile or the maximum migration values. The mean intake of S was calculated to be 0.122 μg/kg bw/d or 0.169 μg/kg bw/d. A comparison with the provisional Tolerable Daily Intake (TDI) of 40 μg/kg bw/d (established by JECFA in 1984) led to the conclusion that exposure to S via food is of no concern for children.

Apart from exposures via food packaging materials, consumers are also exposed to S in natural food items. S occurs in unpackaged food at concentrations near the limit of detection (0.1 μg/kg food) to typically 200 μg/kg (e.g. in olive oil) although levels up to 5 mg/kg have been reported in some mouldy cheeses (Tang et al., 2000). The highest concentrations have been found in cinnamon, ranging from 170 μg/kg to 34 mg/kg (Steele et al., 1994).

2.2. Point of departure

The first step in the derivation of a SML is the definition of SELs for consumers to migrants (herein S) from packaging into food. The calculation of a SEL is generally based on the NOAELs/LOAELs, the points of departure, obtained in experimental animals or epidemiological studies. In studies on experimental animals the selection of a NOAEL or LOAEL is straightforward, as these are defined by the doses selected for the experiment.

Both ECHA (2012) and ECETOC (2010) specifically note that differences exist in the nature of data from animal versus epidemiological studies. In animal tests the doses are predefined leading to precise values for the NOAEL and the LOAEL. The true threshold apparently lies somewhere between the two values. In the case of epidemiological studies, exposures generally cannot be exactly defined and rather exposure categories forming a continuum are estimated. As a consequence, epidemiological data do not directly allow to establish the exact NOAEL, but only to approximate the