

2-Ethylhexanoic acid in baby food and fruit juices packed in glass containers

Expert opinion of BfR of 20 July 2004

Contamination with 2-ethylhexanoic acid (2-EHA) was found during studies by Würzburg University in 28 out of 35 samples of baby food and fruit juices for infants. The contamination stemmed from the lids of jars and bottles in which the foods and fruit juices had been packed. Salts of 2-ethylhexanoic acid are used as stabilisers during the production of sealing compounds in order to render the seals thermo-stable. The acid probably comes from these salts. At higher doses 2-EHA is embryotoxic in animal experiments.

BfR has subjected these findings to a provisional health assessment. It is not possible to give a definitive assessment of the health risk because of the limited amount of exposure data available up to now. In the opinion of the Institute, the maximum level detected of 3.2 mg 2-EHA per kg food might be harmful given the possible additional formation of 2-EHA from plasticizers in the body. The contamination identified in most samples was less than 0.6 mg per kg food and is safe according to BfR. However, in order to be able to undertake a definitive assessment of the health risk, BfR considers that further studies involving glass-packed foods for contamination with 2-EHA are necessary.

BfR is of the opinion that alternative safe stabilisers should be used for the production of sealing compounds for food packaging.

Subject of the assessment

A working group of Würzburg University found 2-ethylhexanoic acid (2-EHA, CAS No. 149-57-5, PM Ref. Nos. 17040 and 54120) in baby food and in fruit juices packed in glass containers with metal lids (Elss, S., Grünwald, E., Richling, E., Schreier, P.: "Occurrence of 2-ethylhexanoic acid in foods packed in glass jars", Food Add. Contam. 21 (8), 811-814). In parallel studies involving the sealing compounds used in the lids, it was observed that the contamination of the foods had been caused by the migration of 2-EHA from the sealing compounds in the metal lids.

Result

According to the knowledge available to BfR, the observed migration of 2-EHA to food can be attributed to the use of 2-EHA salts as thermo-stabilisers for PVC.

EHA is of low acute toxicity and has no genotoxic potential. However, because of its embryotoxic effect it is labelled as "R 63". Given the limited amount of data available on levels of 2-EHA in foods, it is only possible to undertake a provisional risk assessment. Based on the maximum level measured (3.2 mg 2-EHA/kg) and bearing in mind possible, additional formation of 2-EHA from plasticizers, infants could face exposure that cannot be described as safe. Further studies are, therefore, necessary into the levels of 2-EHA in baby food.

Since 2-EHA could not be detected in 20% of the samples examined, this means that the contamination of baby food with 2-EHA is technologically avoidable.

Reasons

Risk assessment

Agent:

2-ethylhexanoic acid (2-EHA), CAS No. 149-57-5, PM Ref. Nos. 17040 and 54120

According to the information available to BfR, calcium/zinc and barium/zinc salts of 2-EHA are used as thermo-stabilisers for PVC, together with co-stabilisers like polyols or epoxy compounds, in order to capture the hydrochloride cleaved during the thermal loading of PVC. The use of 2-EHA metallic soaps to produce PVC for food contact is not explicitly prohibited. However, neither the Commodities Ordinance nor the recommendations of BfR provide a basis for this use.

The Institute assumes that the observed migration of 2-EHA to foods is due to the use of these substances.

Hazard potential:

Given the lack of toxicological data, 2-EHA has been classified by SCF and/or by EFSA in List "6 B" without indicating a migration limit. This list contains substances that are suspected, because of their chemical structure, of having toxicological (but not carcinogenic) properties. However, for none of these is sufficient data available for an assessment. A toxicological assessment of 2-EHA is available from the employers' liability insurance association of the chemical industry (BG Chemie, 2000). According to Directive 67/548/EEC, 2-EHA is classified as "R_E3" because of its possible embryotoxic effect in humans and labelled as "R 63" (possible risk of harm to the unborn child) according to the Dangerous Substances Ordinance.

2-EHA is quickly resorbed orally, dermally and inhalationally and almost fully excreted mainly in urine. As in the case of fatty acids, degradation mainly takes place by means of peroxisomal β -oxidation. 2-EHA is of low toxicity in the case of acute oral administration (LD₅₀, rat: 2043-3640 mg/kg body weight) and may lead to irritation of the skin and eyes. In humans, cases of irritation of the skin, eyes and respiratory tract have been described. There is no indication for a sensitising potential in humans.

In bacterial test systems, mutagenicity studies produced negative findings. In test systems with mammalian cells, by contrast, the findings were weakly positive (IUCLID, 2000). According to the summary data in the IUCLID data set (2000), cytogenetic and SCE studies involving CHO cells were positive, one SCE test in human lymphocytes was questionably positive and one experiment concerning tritium-thymidine incorporation into the DNA of mouse lymphocytes was negative. Furthermore, BfR is aware of an unpublished micronucleus study on the bone marrow of CD-1 mice which was conducted in compliance with OECD Guideline 474. No significant increase in the micronuclei was observed at doses of 400, 800 or 1,600 mg/kg body weight (Inveresk Research International Ltd, 1994). Furthermore, *in vitro* and *in vivo* genotoxicity data (micronucleus test, dominant lethal test) are available for 2-ethylhexanol which is rapidly and quantitatively converted into 2-EHA in metabolism studies. This data do not indicate any genotoxic potential which means that such an effect of 2-EHA is not likely either (BG Chemie, 2000). As 2-EHA can induce both DNA synthesis (Plant et al., 1998) and inhibition of intercellular communication (Lington et al., 1994) in hepatic cells, a tumour-promoting potential in rodents – comparable to that of other peroxisome proliferators – cannot be ruled out. The carcinogenic effect of peroxisome proliferators in rodents (e.g. of di(2-ethylhexyl)phthalate, DEHP) is not deemed to be relevant for humans. Moreover, threshold values are assumed for non-genotoxic carcinogens below which there is no tumour promotion. Based on the documents at BfR's disposal, carcinogenicity studies are not available for 2-EHA (UCLID, 2000; own literature search).

Following sub-chronic oral administration of 2-EHA, critical effects like liver changes (higher relative liver weight, histological changes in hepatocytes) were observed in rats and mice and histological renal tubule results were observed in mice. Furthermore, statistically significant, higher cholesterol values were found in all treated male rats (61, 303 and 917 mg/kg body weight/day) and in male and female mice in the middle and high dose groups (885 - 3139 mg/kg body weight/day). In rats the maximum dose with no adverse effect (NOAEL) was 61 mg/kg body weight/day (Juberg et al., 1998). No chronic studies for 2-EHA are available.

Various studies on reproduction toxicity have produced indications of an embryotoxic effect of 2-EHA. After oral administration, NOAEL values for maternal toxicity and foetotoxic effects of 2-EHA were determined in rabbits at 25 and ≥ 250 mg/kg body weight/day and in rats at 250 and 100 mg/kg body weight/day (Hendrickx et al., 1993). The foetotoxic findings in rats were based on a reduced skeleton ossification at the next higher dose (250 mg/kg body weight/day). No teratogenic effects were observed in this study. In comparison with the structural isomer valproic acid, a known human teratogen, 2-EHA does have similar reproductive effects at maternal toxic doses in animal experiments but a far lower potency.

Exposure:

Up to now, only very limited information is available on the occurrence of 2-EHA in foods.

The Würzburg working group determined levels of EHA in baby food from “non-detectable” (detection limit of the analytical method is not stated) up to 3.2 mg/kg. In 15 out of 20 samples concentrations between 0.25 and 0.5 mg 2-EHA/kg were found. 2-EHA could not be detected in 4 samples. The maximum value of 3.2 mg 2-EHA/kg was only measured in one sample. Furthermore, the following levels of 2-EHA were determined in fruit juices: In 3 out of 15 samples 2-EHA was not detectable. In 12 samples the levels were between 0.01 and 0.59 mg 2-EHA/l. Moreover, BfR was informed that preliminary studies by the Canton laboratory Zurich using a different analytical method confirmed the occurrence of 2-EHA in baby food in jars (oral communication).

From the data available up to now on 2-EHA in baby food, in the worst case scenario a dose of 0.3 mg 2-EHA/kg body weight/day could be derived from the maximum value of 3.2 mg 2-EHA/kg food at a daily intake of 700 g baby food by a child weighing 7.5 kg (assumptions for estimated exposure cf. EFSA expert opinion on SEM, 2003). If a level of 0.6 mg 2-EHA/kg food is assumed for the estimated exposure, which constitutes the maximum value for the 34 of the 35 samples examined, this would lead to a dose of 0.06 mg 2-EHA/kg body weight/day.

2-EHA could not be detected in 7 out of the 35 samples. This leads to the conclusion that contamination of baby food and fruit juices that are filled into glass containers with metal lids is technologically avoidable. As the samples in the submitted publication are not characterised, it is not possible to clarify whether these results can perhaps be attributed to one manufacturer. Given the low number of samples the study results available up to now for baby food and fruit juices cannot yet be considered as sufficient for the general estimation of exposure to 2-EHA. Furthermore, it must be examined whether there are also migrations of 2-EHA from sealing compounds to other foods, which are placed on the market in the packaging systems concerned.

It cannot be ruled out that 2-EHA is additionally formed from other substances which may be used in the production of plastics for food contact use.

In line with BfR Recommendations V and VI for homopolystyrene and styrene mixture polymers and graft polymers, ethylhexanoic acid can be used as a lubricant. Tin-diethyl hexanoate can be used as a catalyst in line with Recommendation IL "Flexible PUR foam as a padding material for fruit". In accordance with Recommendation XV "Silicons", tin diethyl hexanoate can be used as a hardening agent for silicon resins. BfR is not aware of any data on the formation and migration of 2-EHA to foods from the above materials.

Risk characterisation:

Based on the limited data available, only a provisional risk assessment can be made .

For the risk assessment of 2-EHA it should be considered that esters of various acids with 2-ethyl hexanol used as plasticisers for food contact materials may form 2-EHA in the metabolism of humans , too. For di-ethylhexyladipate (DEHA) SCF and/or EFSA has laid down an SML value of 18 mg/kg food. Based on pharmacokinetic data from humans following an oral administration of 46 mg DEHA, on average 8.6% of the dose was excreted as 2-EHA in urine (Loftus et al. 1993). This means that the uptake of DEHA can lead to an additional, internal burden with 2-EHA.

Given the possibility of additional endogenous formation of 2-EHA from plasticizers the margin of safety (MOS) resulting for a child (7.5 kg) exposed to the maximum observed level of 2-EHA (3.2 mg/kg) based on the NOAEL value from the sub-chronic study of 61 mg/kg body weight/day ($61/0.3 = 203$), might not be sufficient. Should such levels be confirmed for foods/baby food, corresponding reduction measures would have to be taken along the lines of precautionary consumer protection. Attention is drawn to the fact that for most of the samples examined (31 out of 35), the maximum concentration of 2-EHA was below 0.6 mg/kg food. For a child (7.5 kg body weight) this means a dose of 0.06 mg 2-EHA/kg body weight/day. Based on the resulting MOS of at least 1,000 there are no health concerns.

Measures

2-EHA could not be detected in 7 out of the 35 samples. This leads to the conclusion that contamination of baby food and fruit juices filled into glass containers with metal lids is technologically avoidable.

In sealing compounds for metal lids, other metallic soaps could be used as PVC stabilisers instead of the 2-EHA salts like, for instance, the salts of n-octanoic acid (PM/Ref. No. 41960) or stearic acid (PM/Ref. No. 89040) are already included in the "Incomplete List of Additives" of the Commodities Ordinance. N-octanoates and stearates are already used for these purposes. It should, therefore, be possible to make corresponding amendments to formulations.

Further studies on the levels of 2-EHA in foods, in particular in baby foods and fruit juices, are needed in order to be able to proceed to a definitive risk assessment.

References

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