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SCIENTIFIC COMMITTEE ON FOOD

SCF/CS/PM 3243 Final
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Opinion on Bisphenol A diglycidyl ether (BADGE)

(expressed on 24 March 1999)

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Terms of Reference

To re-evaluate Bisphenol A diglycidylether (BADGE) in the light of new toxicological and analytical information and of previous opinions.

Background

Bisphenol A diglycidyl ether (BADGE, PM/REF. No. 13510; 2,2-[bis(4-hydroxyphenyl)propane bis(2,3-epoxypropyl) ether, CAS No. 1675-54-3) was previously evaluated by the Committee in November 1986 as a monomer used in the production of plastic food contact materials (1). At that time it was classified into List 4A[1]. The compound was subsequently included in the Commission Directive on monomers 90/128/EEC with the requirement that it should not be detectable in food at the detection limit of 20 µg/kg food, analytical tolerance included, or that the residual content in the plastic should not exceed 1 mg/kg (2).

Surveys carried out in 1995-1996 by official enforcement laboratories in several European countries (UK, Switzerland, Germany, Netherlands, Austria, Italy, Denmark) had revealed high migration (>20 µg/kg food) of BADGE in certain food products packed in internally coated cans. Levels exceeding 1 mg/kg food were found in more than 10% of European samples. Because of the lipid solubility of BADGE efforts had focussed on fat-containing foods, mainly fish-in-oil. As a consequence of these findings these products were withdrawn from sale in Switzerland.

The Committee had been receiving for some time already further information from industry to allay some of the concerns which had resulted in the original restrictive limit on the migration of BADGE. In the light of this situation and the recent action of the Swiss authorities regarding residues of BADGE in canned food the Commission now requested the Committee to re-examine urgently the available data on BADGE. The Commission was supported in this action by a similar request from the packaging industry.

The result of the re-examination was published as an opinion on BADGE by the Committee in June 1996, when the Committee concluded that the substance was to be moved from List 4A to List 7[2] and that additional toxicological data[3] should be supplied with a deadline of two years. The Committee also concluded that in the meantime an upper limit of 1 mg/kg food as a

[1] Definition of List 4A: substances for which an ADI or TDI could not be established, but which could be used if the substance migrating into foods or food simulants is not detectable by an agreed sensitive method.

[2] Definition List 7: substances for which some toxicological data exist but for which an ADI or TDI could not be established. The required additional information should be provided.

[3] [A)] test for chromosomal damage in rodent bone marrow such as a micronucleus assay or a metaphase analysis. If the result of this test is negative, a test for DNA damage/repair in another target tissue, e.g. unscheduled DNA synthesis in rat liver and [B)] an adequate oral 90-day study.

temporary restriction for the specific migration of BADGE and its hydrolysis products should be enforced (3).

Following a subsequent request of the Commission to provide a more detailed explanation of the above opinion with respect to the change in classification and the inclusion of the hydrolysis products in the upper limit for the temporary restriction of the specific migration, the Committee published in June 1997 a further opinion entitled "Clarification and Explanation of the SCF's Opinion of 7th June 1996 on BADGE" (4). In this latter opinion the Committee also noted that chlorohydrins as reaction products of BADGE had been detected very recently in some special can coatings and in foodstuffs processed in epoxyresin-coated cans and that these substances were of concern because of their structural analogy to the genotoxic monochloropropanediol and other chloropropanols of relatively high biological activity. This issue was to be addressed by the Committee as soon as confirmation of the presence of these chlorohydrins and their levels in canned food was received.

Discussion

Usage

The Committee had initially been informed, that BADGE was a starting substance of many epoxy resins currently used as internal can coatings. It was informed later about the use of BADGE as an additive, functioning as a stabiliser and plasticiser in vinylic organosols (blends of PVC and epoxy resins) and as a performance enhancer of polyester-based internal can coatings. This use as an additive implied that some of the BADGE would remain unreacted and thus be liable to migrate into any foodstuffs in contact with such coatings, particularly fatty foods. Three types of cans responsible for the highest migration levels were identified: deep-drawn two-piece cans; easy-open lids; and cans for aggressive foodstuffs. The corresponding internal coatings consisted mostly of vinylic organosols and less frequently of polyester-based varnishes.

Chemical structures

The chemical structures of BADGE (CAS No: 1675-5-43), its hydrolysis products BADGE.H_2O and BADGE.$2H_2O$ as well as the chlorohydrins BADGE.HCl, BADGE.2HCl, and BADGE.HCl.H_2O, the reaction products of BADGE, mentioned in this opinion are shown in Annex 1.

Analytical data

Since the previous opinions of the Committee more information has become available concerning the migration values of BADGE, its hydrolysis products and the reaction products of BADGE under different circumstances.

Analytical surveys, conducted throughout Europe during 1997-1998 revealed that migration values of BADGE into canned food had reduced dramatically, when compared to the situation which existed in 1995-1996. In these enforcement campaigns, which focussed on those canned foods found in the earlier surveys to have yielded the highest BADGE migration values, only a minority of samples (0%-3%, largely representing old stock) exceeded the temporary specific

migration of 1 mg BADGE/kg food, whilst a large proportion (30%-80%) gave analytical results which were below 0.02 mg BADGE/kg food (5).

In canned homogeneous aqueous foodstuffs, e.g. beverages, BADGE and its monoepoxy hydrolysis product (BADGE.H_2O) were hardly detectable and mathematical modelling over the shelf life has confirmed, that in practice only the bisdiol (BADGE.$2H_2O$) is expected to survive in this type of canned food. In canned inhomogeneous aqueous foods, e.g. beans, asparagus, corn, etc., low levels of BADGE.H_2O and of BADGE itself can be found, particularly if the presence of a lipophilic phase protects BADGE from hydrolysis.

Experiments with human gastric simulants showed that BADGE and its monoepoxy hydrolysis product are converted to the corresponding mono- and bisdiols. In such studies effects of lipids on the rate of hydrolysis were also noted, whereby the presence of fat dramatically reduced the reaction yield. Gentle mixing, simulating stomach conditions, equally led to a poor yield of hydrolyis products. However, in the presence of an emulsifier the protective effect of fat was reduced. In studies on model foods containing various proportions of fats emulsified in water, there was also evidence for a protective effect of fat against the hydrolysis of BADGE and of its monoepoxy derivative. In view of these findings it is impossible to extrapolate with any certainty the hydrolysis rates from these model experiments to the situation in canned foods.

Two chlorohydrins (BADGE.HCl, BADGE.2HCl) have now been shown to be formed from the reaction of BADGE with any chloride ions present during curing (processing at high temperatures) of vinylic organosol coatings and especially when over-curing coatings. These chlorohydrins can migrate from the internal coatings of cans into the contained food. The same compounds have been identified in low concentrations in inhomogeneous aqueous canned foods. They are also formed from migrated BADGE, when salty foods are processed in coated cans. The same compounds were reported as having been formed from BADGE exposed to simulated gastric juices in quantities that depend on the exposure time. However there is contradictory information with respect to the rate of formation of the chlorohydrins and of their subsequent hydrolysis to BADGE.$2H_2O$ under different pH conditions.

Toxicological aspects

In its 1996 evaluation the Committee considered BADGE to be mutagenic in several *in vitro* assays using different endpoints, but the then available studies were inadequate to demonstrate lack of activity *in vivo*. This aspect has been clarified by the provision of additional data and the non-genotoxicity *in vivo* in liver and bone marrow has now been demonstrated. The *in vivo* covalent DNA-binding studies indicate the presence of a weak DNA-binding capacity of BADGE when applied directly to mouse skin. This still raises concerns regarding the potential for a similar direct DNA-binding activity of BADGE at the site of gastrointestinal mucosal contact following oral exposure because of the absence of any specific experimental studies covering this aspect. The available oral subacute, one-generation reproduction, and two-generation reproduction studies provide experimental evidence that the ingestion of BADGE has no short-term adverse effect on the histology of the stomach and intestinal mucosa. Furthermore, human epoxide hydrolase has a higher activity than mouse skin epoxide hydrolase. These factors would reduce the importance of the concerns mentioned above (6).

The metabolic data provided evidence for extensive and rapid metabolism of BADGE (6).

The reproduction and teratology studies reviewed in 1996 showed that BADGE did not possess any potential for a toxic effect on reproduction, was not teratogenic, and did not interfere with fertility of the test animals (6).

The chronic toxicity/carcinogenicity studies used dermal exposure in mice and rats to either pure BADGE or technical grade BADGE of different types. None of these studies produced evidence for either dermal or systemic tumourigenic effects. The rat study with pure BADGE showed evidence of hepatotoxicity only (6)

Conclusion

No evidence exists for a systemic tumourigenic effect of topically applied pure or technical BADGE. Pending clarification of any potential for a direct DNA-binding activity of BADGE on the gastrointestinal mucosa following oral exposure and in the absence of an adequate oral chronic toxicity/carcinogenicity study the Committee is still unable to set an ADI or TDI for BADGE and proposes to extend for a period of three years an upper limit of 1 mg/kg food as a temporary restriction for specific migration of BADGE and its hydrolysis products.

In assessing compliance, the restriction should include the sum of migration of BADGE and its monoepoxy hydrolysis product (BADGE.H_2O) when examined in canned food directly or via fatty food simulants. In case of examination via aqueous food simulants the restriction should include BADGE, the monoepoxy (BADGE.H_2O) and the bisdiol (BADGE.$2H_2O$) hydrolysis products of BADGE. In the latter case BADGE.$2H_2O$, which by itself is of minor toxicological relevance, should be determined and included, since in aqueous food simulants more BADGE and BADGE.H_2O would convert to BADGE.$2H_2O$ as compared to the situation in foodstuffs.

As toxicological data on the chlorohydrin derivatives of BADGE are still lacking, the Committee reiterates its concern over their presence in canned foods. The Committee proposes to include the three chlorohydrins BADGE.HCl, BADGE.2HCl, BADGE.H_2O.HCl, which can migrate from the coating or be formed in salty foods, in the upper limit for specific migration of BADGE in addition to the hydrolysis products.

The Committee requires to be provided within three years with the results of DNA-binding studies on tissues of the upper gastrointestinal tract with pure BADGE or alternatively with the results of mutational studies in transgenic rodents to enable it to consider the continuation of the upper limit of 1 mg/kg food as a temporary restriction for specific migration of BADGE and its hydrolysis products.

In addition to the above request, the Committee also requires to be provided within 3 years with the results of either DNA-binding studies or the results of mutational studies in transgenic rodents on all the three named chlorohydrin derivatives of BADGE, unless it can be demonstrated by appropriate *in vitro* studies that these compounds do not possess any genotoxic potential, to enable it to consider the maintenance of this provision for inclusion in the migration limit.

References

1 SCF (1988) Nineteenth series of Reports, EUR 11322, Commission of the European Communities, Luxembourg.

2 Commission Directive 90/128/EEC of 23 February 1990 relating to plastic materials and articles intended to come into contact with foodstuffs. *Official Journal L 75, 21/3/1990 p. 19 -40*

3 CS/PM/2812 Final, June 1996: Opinion on Bisphenol A diglycidyl ether (BADGE), June 1996. SCF (1997). Fortieth series of Reports, GT 07 97652, Commission of the European Communities, Luxembourg.

4 CS/PM/2986-Final, June 1997. Clarification and explanation of the SCF's opinion of 7 June 1996 on BADGE. Forty fourth series of Reports, (in press) or http://www.europa.eu.int/comm/dg24/health/sc/oldcomm7/out05_en.html.

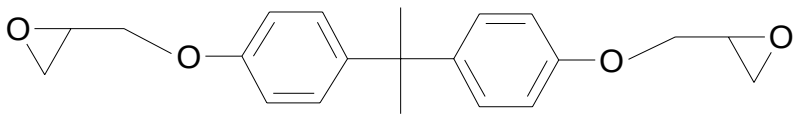
5 CS/PM/3114 Rev.2 /PM/REF 13510: Report on migration of BADGE and of related compounds. dated January 1999.Working Group Document: compilation of background material, including references.

6 CS/PM/3193 Rev.4 /PM/REF 13510: Diglycidyl ether of Bisphenol A (BADGE) Evaluation of toxicology. Dated February 1999. Working Group Document: compilation of background material, including references.

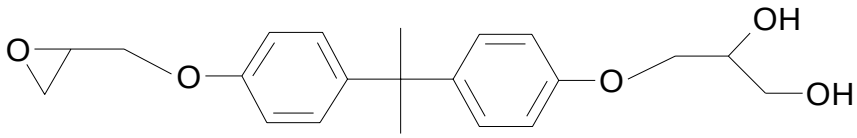
Annex

This annex contains for the purpose of clarification the structural chemical formulas of BADGE and the hydrolysis and chlorohydrin reaction products of BADGE mentioned in this "Opinion on BADGE"

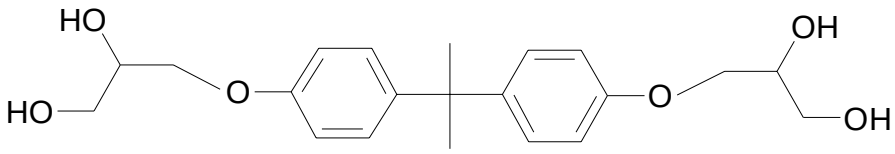
BADGE:



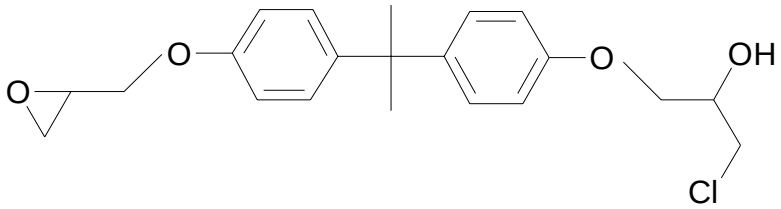
BADGE.H_2O:



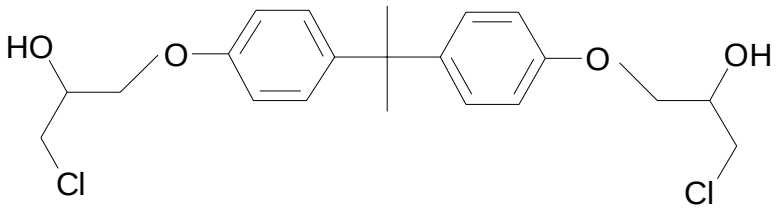
BADGE.$2H_2O$:



BADGE.HCl:



BADGE.2HCl:



BADGE.H_2O.HCl: