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DIRECTORATE-GENERAL HEALTH AND CONSUMER PROTECTION  
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Unit C2 – Management of Scientific Committees; scientific co-operation and networks

**Scientific Committee on Toxicity, Ecotoxicity and the Environment**

Brussels, C2/AST/csteep/**Bisph A HH22052002/D(02)**

**SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND  
THE ENVIRONMENT (CSTEE)**

**Opinion on the results of the Risk Assessment of:**

**BISPHENOL A  
HUMAN HEALTH PART**

**CAS NO: 80- 05- 7  
EINECS NO: 201-245- 8**

**Carried out in the framework of Council Regulation (EEC) 793/93 on  
the evaluation and control of the risks of existing substances<sup>1</sup>**

**Opinion expressed at the 31th CSTEE plenary meeting**

**Brussels, 22 May 2002**

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<sup>1</sup> Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94, which is supported by a technical guidance document.

**CSTEE COMMENTS ON:**

**RISK ASSESSMENT REPORT ON:**

**Bisphenol A**

**Human health**

**CAS No.: 80-05-7**  
**EINECS No.: 201-245-8**

### **Terms of reference**

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report
2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

### **Introduction**

Bisphenol A is a major industrial chemical used in the production of polycarbonates, as a component in epoxyresin and a variety of other applications. Annual production within the EU amounts to app. 800 000 tonnes. Human exposure to bisphenol A may occur during production and application of bisphenol A and during processing of bisphenol A containing products. In addition, bisphenol A may leach from polycarbonates and epoxy resins used in food cans and bottles to result in possible widespread exposure of the general public to low daily doses.

### **General comments**

The health part of the document is of excellent quality, it is comprehensive and follows the TGD. Since some of the occupational exposure scenarios results in low MOS, CSTEE agrees with conclusion iii) for these scenarios.

### **Specific comments**

A broad database on toxicity and human exposure for bisphenol A is available for evaluation and health risk assessment. The document uses both published data from peer reviewed journals, industry reports and abstracts as a basis for the evaluation.

## **HUMAN HEALTH**

### **1. Exposure assessment**

Human exposure to bisphenol A may occur during occupational scenarios and due to migration of bisphenol A from food contact material into food. For the occupational scenarios, inhalation of bisphenol A in form of dust is the most relevant pathway of exposure expected; exposure estimates for inhalation and dermal exposure are both based on measured data from industry and on modeling for the most relevant occupational exposure scenarios. The RAR describes the problems with the measured data due to different sampling design and methodology. For environmental human exposures, dietary exposures are most relevant. The process used in the RAR for estimating oral exposure of consumers is highly conservative and predicts a cumulative daily exposure to bisphenol A with food of up to 0.6 mg/person, mainly from wine consumption and canned food. A recent dietary exposure assessment performed by the Scientific Committee on Food results in a much lower estimated intakes from dietary exposures. The use of these more realistic exposure estimates, would, however, not change conclusion ii) for consumer exposure using the endpoints "liver toxicity" and "effects on fertility" since MOS are already large.

### **2. Effects assessment**

#### ***Toxicokinetics***

The toxicokinetics of bisphenol A have mainly been studied in the rat. After oral administration, absorption of bisphenol A from the gastro-intestinal tract is rapid and complete, absorption after dermal exposure is limited. Due to an intensive first-pass metabolism in the liver to give bisphenol A glucuronide (which is devoid of oestrogenicity), bioavailability of free bisphenol A after oral administration in the rat is limited. Bioavailability of free bisphenol A after subcutaneous or intraperitoneal application is higher and the differences in biotransformation and bioavailability may explain the large differences in the sensitivity of rodents to bisphenol A oestrogenicity seen in studies when applying different routes of administration. CSTE agrees that the potential of bisphenol A for transfer to the fetus and for bioaccumulation is low.

#### ***Acute toxicity***

The acute oral and dermal toxicity of bisphenol A has been studied in rats, mice and rabbits. The available data from the studies show that the acute toxicity of bisphenol A is low with LD<sub>50</sub>-values > 2 000 mg/kg. By inhalation, the maximal attainable concentration of bisphenol A in air (170 mg/m<sup>3</sup>) did not produce death in rats after inhalation exposure for 6 hours.

#### ***Irritation and corrosivity***

Bisphenol A is not irritating to skin, but has the potential for severe eye irritation. The CSTE agrees that bisphenol A is not corrosive.

### ***Sensitizing properties***

Repeated skin contact with bisphenol A in humans has resulted in skin lesions and occupational exposure to bisphenol A may result in photosensitisation. These observations in humans are supported by limited results from animal studies. The conclusions that bisphenol A "is producing skin responses consistent with those of a skin sensitizer" is unclear, the RAR should give a more defined conclusion. In the risk characterisation, bisphenol A is treated "like" a skin sensitizer. Conclusion iii) regarding control of skin exposure for all occupational scenarios is supported by the CSTE.

### ***Repeated dose toxicity***

A number of repeated dose studies on bisphenol A in mice and rats using oral administration and a 90-day study in rats after inhalation exposure are available for evaluation.

The effects seen in the inhalation study with a maximal concentration of 150 mg bisphenol A/m<sup>3</sup> were decreased absolute liver and kidney weights and slight inflammation of the upper airways. The CSTE agrees with the NOAEL of 10 mg/m<sup>3</sup> derived from this study.

Dietary administration of bisphenol A in mice indicates that the liver is a target organ of bisphenol A in this species resulting in changes in size and nucleation of hepatocytes. A NOAEL for these effects could not be defined from the available data and a LOAEL of 120 mg/kg/day is derived.

### ***Genotoxicity***

*In vitro*, bisphenol A was not mutagenic in several Ames tests with Salmonella typhimurium strains TA1535, TA1537, TA100, TA98, TA97a or TA102 and E. coli WP2 and WP2 uvrA with or without liver enzyme preparations. It did not induce gene conversions in yeasts. It was not genotoxic in a standard mouse lymphoma L5178Y/TK+/- assay with or without metabolic activation, but showed inconclusive results with the microtitre method. Bisphenol A failed to induce gene mutations at the hprt locus in V79 cells and at the Na<sup>+</sup>/K<sup>+</sup> ATPase locus or the hprt locus in SHE cells.

Sister chromatid exchanges or chromosomal aberrations were not induced in CHO cells in the presence or absence of metabolic activation or, without metabolic activation, in SHE cells and an epithelial type rat liver cell line (RLI). In another study with CHO cells, not cited in the RAR (Hilliard, 1998), chromosome aberrations were only seen at doses with steeply increasing cytotoxicity.

In assays without metabolic activation, bisphenol A was shown to have an effect on microtubules and to induce aneuploidy in V79 and SHE cells. CREST-positive micronuclei were found in V79 cells.

After oxidation or metabolic activation, bisphenol A was capable of forming adducts with deoxyguanosine-3'-monophosphate (dGMP) or isolated rat liver DNA, and DNA adducts were also found in SHE cells. In bacteria, bisphenol A induced DNA damage, but not protein damage, oxidative damage or membrane damage (Gu, 2002; not mentioned in the RAR). Bisphenol A was shown to influence the

transcriptional activities of thyroid hormone receptors in transfected human embryonic kidney cells (Moriyama, 2001; not mentioned in the RAR). Bisphenol A did not induce unscheduled DNA synthesis in rat hepatocytes.

In an *in vivo* study performed in accordance with current guidelines, bisphenol A did not induce micronuclei in bone marrow cells of ICR mice orally dosed with up to 2 000 mg/kg bw. No mutagenic activity was observed in a dominant lethal study in rats, which is only available as an abstract. In rats, bisphenol A was shown to induce liver DNA adducts after single intraperitoneal administration or repeated oral doses of 200 mg/kg bw and day. Bisphenol A showed no mutagenic effects in the *Drosophila* sex-linked recessive lethal test.

Although there is some evidence for a genotoxic activity *in vitro*, bisphenol A was not genotoxic *in vivo* and there is no evidence from animal carcinogenicity studies for a significant carcinogenic effect. The DNA-adducts were considered as of no concern to human health as there were no positive results for gene mutation and clastogenicity in cultured mammalian cells.

The CSTEE, therefore, agrees with the overall conclusion that bisphenol A has no significant mutagenic potential *in vivo*.

### **Carcinogenicity**

No epidemiological data relevant to the carcinogenicity of bisphenol A are available.

Bisphenol A was tested for carcinogenicity in 2-year feeding studies in F344 rats and in B6C3F1 mice (rats: 0, 1 000, 2 000 ppm; mice: 0, 1 000, 5 000 ppm [male]; 0, 5 000, 10 000 ppm [female]).

A small, not statistically significant increase in leukaemias was observed in male and female rats. This, as well as the slight increases in the frequency of mammary gland fibroadenomas in male rats was considered as a chance finding. An increased incidence in benign Leydig cell tumours seen in male rats was within historical control limits.

In male mice fed 1 000 or 5 000 ppm bisphenol A with the diet, the incidence of lymphomas was slightly increased in the low dose, but not in the high dose.

Cell transformation assays with bisphenol A were either negative (3T3, SHE cells) or inconclusive (SHE cells), since no dose-response relationship could be established.

Based on the overall evaluation of the available data, including those from repeated dose and mutagenicity studies, the CSTEE agrees with the assessor that bisphenol A does not have a significant carcinogenic potential

### **Reproductive and developmental toxicity**

The weak oestrogenicity of bisphenol A, known for more than 60 years, and the potential widespread human exposure have resulted in a renewed interest in potential effects of bisphenol A due to "endocrine modulation". A large number of studies in rats and mice and in different *in vitro* systems are available for evaluation, these are comprehensively summarized in the RAR.

Consistently, the *in vitro* data on oestrogenicity show that bisphenol A is a weak oestrogen with an activity 3 – 5 orders of magnitude less than that of the reference oestrogen 17 $\beta$ -oestradiol. In rodents *in vivo*, high doses of bisphenol A are required to induce oestrogenic responses after oral administration in rats (> 500 mg/kg bw) and in mice (> 300 mg/kg bw), subcutaneous and intraperitoneal administration results in effects at significantly lower doses (> 50 mg/kg bw).

Studies performed according to established toxicity testing guidelines under formal quality control observe effects on development and reproduction after application of high doses. The effects of bisphenol A on fertility and reproductive performance were studied in a two-generation and a multi-generation in the rat and a continuous breeding study in the mouse. Effects on reproduction and fertility were seen in rats in the three-generation study at 500 mg/kg bw. In mice, adverse effects on fertility were seen at dietary doses of bisphenol A of 600 mg/kg bw and a NOAEL of 438 mg/kg was derived from the study. A NOAEL of 50 mg/kg/day is derived in the RAR from the results of the multi-generation study for effects on fertility. The CSTEE agrees with this NOAEL.

Results from standard developmental toxicity assays in rodents resulted in the establishment of a NOAEL of 640 mg/kg for foetal effects in rats and 1 000 mg/kg in mice. In the rat multi-generation study, decreased pup body weight gains and delays in the acquisition of developmental landmarks were seen at 500 mg/kg bw with no effects seen at 50 mg/kg bw. A “provisional” NOAEL of 50 mg/kg bw is derived for effects on development, the CSTEE agrees with this value.

However, a number of studies using non-standard protocols have reported effects of bisphenol A administration on development using substantially lower doses than the studies performed according to testing guidelines. The RAR critically describes the many weaknesses (lack of repeatability, problems with experimental design and statistical evaluation, poor reporting) of the low dose studies. The CSTEE agrees with the conclusion of the RAR that there is no convincing evidence that low doses of bisphenol A have effects on developmental parameters in offspring and remarks that effects observed are not adverse.

The conflicting data from studies using low doses, however, do raise uncertainties. The uncertainties on possible low dose effects of bisphenol A, albeit based on a limited number of studies using non-standard protocols, result in conclusion i) requesting further research. A recent report (NTP, 2001) comes to the same conclusion.

The CSTEE questions if the uncertainties in the database on the developmental toxicity of bisphenol A can be resolved by further studies limited to effects of bisphenol A since, for this compound, a number of high quality studies on the reproductive and developmental effects of bisphenol A are already available and do not support low-dose effects. Further work should be aimed to improve our understanding of factors influencing outcome and variabilities in developmental toxicity studies (housing, diet, species, strain and sub-strain, study design and issues of species extrapolation).

### **3. Risk characterisation**

#### ***Genotoxicity/Mutagenicity***

Because that bisphenol A is not mutagenic *in vivo*, this endpoint was not considered further in the assessment.

**Carcinogenicity**

Because there is no convincing evidence that bisphenol A is carcinogenic, this endpoint was not considered further in the assessment

**Workers**

The exposure and effects assessment for bisphenol A result in low MOS for certain occupational exposures and conclusion iii) which is supported by CSTE.

**Consumers**

As already stated above, the estimated exposures of consumers to bisphenol A are very conservative ; a more recent exposure assessment of the SCF predicts much lower exposures of consumers. Integration of these revised exposure estimates would result in a further increase in the MOS, but will not change conclusion ii) for all exposure scenarios for liver toxicity and fertility.

**References**

Gu M.B. et al.: Toxicity monitoring and classification of endocrine disrupting chemicals (EDCs) using recombinant bioluminescent bacteria. *Chemosphere* 46, 289-294 (2002)

Hilliard C.A. et al.: Chromosome aberrations *in vitro* related to cytotoxicity of nonmutagenic chemicals and metabolic poisons. *Env. Mol. Mutag.* 316-326, 1998

Moriyama K. et al.: Bisphenol A inhibits transcriptional activity mediated by the thyroid hormone receptors. *Teratology* 63, 38A, 2001

NTP, 2001, National Toxicology Program's report of the endocrine disruptors low dose peer review.