SCOEL/SUM/113
May 2004

Recommendation from the Scientific Committee on

Occupational Exposure Limits for

Bisphenol-A

8 hour TWA:	10 mg/m^3
STEL:	none
Additional classification:	none

Substance identification:

Chemical Name bisphenol-A

CAS Registry Number: 80-05-7

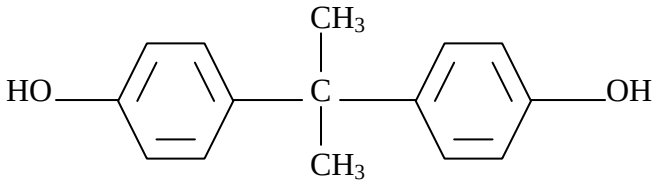
EINECS Number: 201-245-8

IUPAC Name: 2,2-bis(4-hydroxyphenyl)propane

Molecular Formula: $C_{15}H_{16}O_2$

Molecular weight: 228.29

Structural formula:



EU Classification: Repr. Cat. 3; R62 Possible risk of impaired fertility.
Xi;R37-41 Irritating to respiratory system.
Risk of serious damage to eyes.

R43 May cause sensitization by skin contact

Parameter	Value	Comments
Physical state at normal temperature and pressure	White solid flakes or powder	Depends upon manufacturing process
Melting point	155-157°C	Depends upon manufacturing process
Boiling point	360°C at 101.3 kPa	Decomposition is also likely
Relative density	circa 1.1-1.2 kg/m^3 at 25°C	
Vapour pressure	5.3×10^{-9} kPa	
Solubility in water	300 mg/l	
Partition coefficient	Log Kow circa 3.3-3.5	
Flash point	circa 207°C	
Autoflammability	circa 532°C	
Explosive limits (in air)	Minimum explosive concentration 0.012 g/l with oxygen > 5%	
Oxidising properties	Not an oxidising agent	

Occurrence and Use:

Four companies within the EU manufacture bisphenol-A. There are a total of six production sites based in Germany, The Netherlands, Belgium and Spain. The total amount of bisphenol-A manufactured within the EU, based upon submissions to CEFIC by the manufacturers, is estimated at approximately 700,000 tonnes/year). According to EU statistics in 1997 the total imports of bisphenol-A into the EU were 8,010 tonnes/year (EU RAR 2002).

Bisphenol-A is manufactured from phenol and acetone by an acid or alkaline catalysed condensation reaction. Its uses in the EU are shown below (EU RAR 2002):

Use Pattern Data	Tonnes/year	Percentage of EU consumption
Polycarbonate production	486,880	71.1
Epoxy resin production	171,095	25.0
Phenoplast resins	8,800	1.3
Unsaturated polyester resin production	3,000	0.4
Can coating manufacture	2,460	0.4
Use PVC production and processing	2,250	0.3
Alkyloxylated bisphenol-A manufacture	2,020	0.3
Thermal paper manufacture	1,400	0.2
Polyols/Polyurethane manufacture	950	0.1
Modified polyamide production	150	<0.1
Tyre manufacture	110	<0.1
Brake fluid	45	<0.1
Minor uses	5,990	0.9
EU Consumption	684,650	

Health Effects:

Toxicokinetics

The toxicokinetics of BPA has been well studied in rats both *in vivo* and *in vitro*, and has been investigated to a lesser extent in mice, cynomolgus monkeys and humans (see EU RAR 2002; Domoradski et al 2002; Kurebayashi at al 2003; Volkel et al 2002). In the species studied (rats, mice, monkeys, humans), the available evidence suggests that following oral administration, BPA is rapidly and extensively (about 85-100% of administered dose) absorbed from the gastrointestinal tract. An *in vitro* dermal absorption study using human skin found limited (about 10%) absorption. There are no data on the toxicokinetics of bisphenol-A following inhalation exposure but it is assumed that appreciable absorption would occur.

Regarding the distribution of absorbed bisphenol-A to tissues, after oral dosing BPA is removed rapidly from the blood by first pass metabolism in the liver. In adult rats it has been estimated that no more than 10-20% of the administered dose of free BPA is available to other tissues. A study in pregnant mice given bisphenol-A subcutaneously detected free bisphenol-A in the placenta and fetal tissues.

In terms of metabolism, in all species studied the major metabolic pathway involves conjugation of bisphenol-A to glucuronic acid. In addition to the glucuronidation pathway, *in vivo* and *in vitro* studies suggest that bisphenol-A may be subject to limited oxididation to bisphenol O-quinone by cytochrome P450, and also to conjugation to sulphate.

The major route of elimination in the rat and mouse is via the faeces. The available data indicate that the percentage of the administered dose recovered in the faeces is in the range 50% to 83%. Urinary excretion is of secondary importance in the rat, with 13% to 42% of the administered dose being recovered in the urine. Over 7 days post-dosing 70-80% of the administered dose was eliminated in the faeces in rats. Elimination was rapid; the majority of the dose was excreted by 72 hours post-dosing. A sex difference was also observed in rats for urinary elimination, with females excreting approximately twice as much radioactivity (24-28%) than males (14-16%). In addition, a strain difference was observed in elimination, with female F344 rats excreting approximately twice as much radioactivity in the urine than female CD rats.. Data from a number of studies suggest limited excretion of BPA in the milk. However, the data do not allow a reliable quantitative determination to be made.

In contrast to the findings in rodents, in cynomolgus monkeys given BPA orally most of the administered dose (82–85%) was recovered in the urine, with only 2-3% of the dose being recovered in the faeces. In a limited study in human volunteers given a low dose of BPA orally, the administered dose was completely recovered in the urine as BPA-glucuronide. These interspecies differences in the main route of excretion of BPA may be due to differences in the thresholds for biliary elimination: it is noted that the molecular weight of BPA-glucuronide is above the threshold in rats (approximately 350 Daltons) but below the threshold in humans (about 550 Daltons).

Effects of single exposure

No useful information is available on the effects of single exposure to bisphenol-A in humans. Oral LD_{50} values beyond 2000 mg/kg are indicated in the rat and mouse, and dermal LD_{50} values above 2000 mg/kg are evident in the rabbit (Hazleton Laboratories 1985; NTP 1982; Mellon Institute 1948,1965). For inhalation, a 6-hour exposure to 170 mg/m^3 (the highest attainable concentration) produced no deaths in rats; slight and transient slight nasal tract epithelial damage was observed (Nitschke et al, 1985a). These data indicate that bisphenol-A is of low acute toxicity by all routes of exposure relevant to human health.

Irritancy

Limited human anecdotal information of uncertain reliability is available from written industry correspondence suggesting that workers handling bisphenol-A have in the past experienced skin, eye and respiratory tract irritation (Dow Chemical 1957; Du Pont 1962). It cannot be determined whether the reported skin reactions were related to skin sensitisation (see below) or irritation. However, a recent well conducted animal study clearly shows that bisphenol-A is not a skin irritant (Leuschner 2000a). A recent well conducted animal study shows that bisphenol-A is an eye irritant; effects persisted until the end of the study (day 28 post-instillation) in 1 of 3 rabbits (Leuschner 2000b). Overall, taking into account the animal and human evidence, bisphenol-A has the potential to cause serious damage to the eyes.

Slight and transient nasal tract epithelial damage were observed in rats exposed to bisphenol-A dust at 170 mg/m^3 (the highest attainable concentration) for 6 hours (Nitschke et al, 1985a). These data suggest bisphenol-A appears to have a limited respiratory irritation potential.

Sensitisation

With respect to skin sensitisation in humans, there are several reports of patients with dermatitis responding to bisphenol-A in patch tests (see EU RAR 2002). However, it is unclear whether bisphenol-A or related epoxy resins were the underlying cause of the hypersensitive state. Anecdotal information indicates skin inflammation in workers handling bisphenol-A, although given the uncertain reliability of this information no conclusions can be drawn from it. In animals, a skin sensitisation test performed to current regulatory standards is not available. The available studies are negative, but the test reports lack detail and no reliable justifications were given for the choice of concentrations used Thorgeirsson and Fregert, 1977; Procter and Gamble Co. 1969) It is possible that the concentrations used in all the available studies were not maximised and a greater response might have been obtained with higher induction and challenge concentrations. Based on the findings from the most robust study, bisphenol-A may possess a skin sensitisation potential, albeit a limited one. Bisphenol-A in the presence of UV light can also elicit skin responses in humans, and reproducible positive results for photosensitisation have been obtained in mouse ear swelling tests (Allen and Kaidbey 1979; Maguire 1988; Gerberick and Ryan 1990).. Therefore, examination of the available human and experimental animal studies leaves the picture somewhat unclear as to whether one or more of the following are properties of bisphenol-A; (1) orthodox skin sensitisation (2) photosensitisation (3) bisphenol-A eliciting a response in people previously skin sensitised to another substance (e.g. epoxy resins). Thus, the precise nature of the hazardous properties of bisphenol-A on the skin is unclear, but clearly skin reactions can be a potential consequence of repeated skin exposure in humans. Overall, taking all of the data available into account, bisphenol-A is considered capable of producing skin sensitisation responses in humans. There are no data from which to evaluate the potential of bisphenol-A to be a respiratory sensitiser.

Effects of repeated exposure

No useful information is available on the effects of repeated exposure in humans. In animals there are no data relating to repeated dermal exposure. Repeat inhalation studies are available in the rat (Nitschke et al 1985b, 1988). The principal effect was the same as that observed following a single exposure - slight upper respiratory tract epithelium inflammation. Very slight to slight inflammation and hyperplasia of the olfactory epithelium were observed following exposure to 50 and 150 mg/m^3 (6 hours/day, 5 days/week for 2 or 13 weeks; 150 mg/m^3 is close to the highest attainable concentration; the particle MMAD was 2-6 microns), and a NOAEL of 10 mg/m^3 was identified in rats in this 13 week study.

Dietary studies in rats produced a decrease in body weight gain and minor changes in organ weight at 100 mg/kg/day and above in 90-day studies (Til et al 1978; NTP

1982). These effects are difficult to interpret in terms of their toxicological significance in the absence of other findings (e.g. histopathological changes). An inconsistent finding of caecal enlargement was seen in some 90 day studies. The caecal enlargement was observed at 25 mg/kg/day and above and was without any associated histological abnormalities. In addition, it was not observed in a 2 year study at doses up to about 140 mg/kg/day or a multigeneration study at doses up to 500 mg/kg/day (NTP 1982; Tyl et al, 2002). Consequently, this is not regarded as a toxicologically significant observation of relevance to humans. Overall, a NOAEL of 74 mg/kg/day has been established for rats from a 2 year study.

Dietary studies in mice consistently indicated that the liver is a target organ in this species with changes being observed in the size and nucleation state of hepatocytes in a 2 year and 90 day studies (NTP 1982; Furukawa et al 1994;. The incidence and severity of these treatment-related multinuclear giant hepatocytes was markedly greater in males than in females. It was not possible to identify a no effect level for males, the effect being observed at all dose levels used from the lowest dose tested of 120 mg/kg/day (2-year study). Even at this lowest dose level a large proportion (84%) of the animals examined showed signs of this effect. In females, a no-effect level of 650 mg/kg/day was identified for these cellular changes in the 2-year study. The mechanism by which changes arise and their significance for human health is not clear but cannot be dismissed as being of no significance. The only other findings in mice were significant reductions in body weight gain at dose levels of 650 mg/kg/day and above. Thus, a LOAEL of 120 mg/kg/day in males for multinuclear giant hepatocytes and 650 mg/kg/day in females for a reduction in body weight gain of unknown magnitude, were identified in a 2 year study.

In a 90 day dietary study in dogs, a no effect level of approximately 80 mg/kg/day was identified, with increases in relative liver weight being the only finding observed at approximately 270 mg/kg/day (General Electric 1976). In the absence of changes in histopathology, this finding is of doubtful toxicological significance.

Mutagenicity

No human data regarding mutagenicity are available. However, bisphenol-A appears to have demonstrated aneugenic potential in vitro, positive results being observed without metabolic activation in a micronucleus test in Chinese hamster V79 cells and in a non-conventional aneuploidy assay in cultured Syrian hamster embryo cells (Pfeiffer et al 1997; Tsutsui et al 1998). Additionally, in cell-free and cellular systems, there is information that shows bisphenol-A disrupts microtubule formation (see EU RAR 2002). Bisphenol-A has been shown to produce adduct spots in a post-labelling assay with isolated DNA and a peroxidase activation system, but it does not appear to produce either gene mutations or structural chromosome aberrations in bacteria, fungi or mammalian cells in vitro (see EU RAR 2002). However, some deficiencies in the conduct of these studies have been noted and the negative results cannot be taken as entirely conclusive. Bisphenol-A does not appear to be aneugenic in vivo, since a recently conducted, standard mouse bone marrow micronucleus test has given a negative result (Shell Oil Company 1999). Bisphenol-A was negative in a briefly reported dominant lethal study in rats but, given the limited details provided, this is not regarded as an adequate negative result. The only other data in somatic cells in

vivo are from a ^{32}P-postlabelling assay, which showed that bisphenol-A is capable of producing DNA adduct spots in rat liver following oral administration. These adduct spots were not characterised fully.

Considering all of the available genotoxicity data, and the absence of significant tumour findings in animal carcinogenicity studies (see below), it does not appear that bisphenol-A has significant mutagenic potential in vivo.

Carcinogenicity

There are no human data contributing to the assessment of whether or not bisphenol-A is carcinogenic. In animals, a dietary carcinogenicity study in two species, F344 rats and B6C3F$_1$ mice, is available (NTP 1982). A small increased incidence of leukaemias was seen in male and female F344 rats along with increases in the frequency of mammary gland fibroadenomas in male rats. These increases were not statistically significant, were slight and in a strain prone to these tumours. An increased incidence in benign Leydig cell tumours seen in male rats was within historical control limits. In mice, a small increased incidence in lymphomas was observed in males, but was not statistically significant and there was no dose-related trend. No increased incidence in any tumour type was observed in female mice. Overall, all of these tumour findings in rats and mice are not considered toxicologically significant. Consequently, it is concluded that bisphenol-A was not carcinogenic in this study in both species. No inhalation or dermal carcinogenicity studies are available, although in repeat exposure inhalation toxicity studies, bisphenol-A did not exhibit properties that raise concern for potential carcinogenicity. Only minimal inflammation was seen in the upper respiratory tract at 50 mg/m^3 in a 13 week study and the severity did not increase up to concentrations close to the maximum attainable concentration in the experimental system used, 150 mg/m^3. Taking into account all of the animal data available the evidence suggests that bisphenol-A does not have carcinogenic potential.

Endocrine modulating activity

Bisphenol-A has been shown to have endocrine modulating activity in a number of in vitro and in vivo screening assays (see EU RAR 2002). The potency of this activity in these assays generally ranged from 3 to 5 orders of magnitude less than that of oestradiol. The available data also indicate that there is a marked strain difference in the response to bisphenol-A in rats. However, there are no data to indicate the underlying reasons for such differences.

It should be noted that these studies investigating endocrine modulating activity are essentially screening tests and many of them employ experimental protocols, which have not undergone any international validation. In addition, many of the available in vivo studies have used parenteral routes of exposure, the relevance of which are uncertain with respect to relevant routes of human exposure.

Effects on reproduction

The effects of bisphenol-A on fertility and reproductive performance have been investigated in three good quality studies: two generation and multigeneration studies in the rat, and a continuous breeding study in the mouse. In the multigeneration study, an effect on fertility (reduction in litter size) was seen in all three generations at the top dose of 500 mg/kg (Tyl et al 2002). Although this effect was seen only at a dose level causing parental toxicity (a reduction in body weight gain (>13%) in both sexes and renal tubule degeneration in females only), it is not clear whether or not the finding could be a secondary consequence of parental toxicity, or a direct effect of bisphenol-A. In the light of this uncertainty, and given that an adverse effect on fertility has been seen in the mouse, it is prudent to assume that bisphenol-A may be having a direct effect on fertility in this study. No effects on fertility were seen at 50 mg/kg. The continuous breeding study in the mouse provides some evidence that bisphenol-A can cause adverse effects on fertility (NTP 1985b). In the F_0 generation, no effects on fertility were seen at 300 mg/kg/day, but at dose levels of approximately 600 mg/kg/day and above, reductions in the numbers of litters produced, litter size and numbers of live pups per litter were observed in each of the 4-5 litters produced. These effects were observed in the absence of significant parental toxicity. In contrast, no adverse effects on fertility were observed in the single litter tested at each dose level from the F_1 generation. A small but statistically significant and dose-related decrease in epididymal weight was seen at all doses in the F_1 generation, but the significance of this finding is uncertain because a comparable effect was not seen in F_0 mice. In spite of the uncertainty, the epididymis is associated with sperm transport and storage, and any reduction in the weight of this organ would be of concern. For risk characterisation purposes, although no effects were seen in the two-generation rat study it is not considered suitable due to the low dose levels employed of 0.2-200 microgrammes/kg/day(Chemical Compound Safety Research Institute 2000). However, this data combined with that for the multigeneration study does provide a comprehensive dose-response range for effects on fertility in the rat. In addition, comparing the rat and mouse data it can be seen that similar toxicological profiles were observed for effects on fertility; effects were seen in both species at approximately the same dose level (i.e. reductions in litter size at 500 mg/kg/day in the rat and at 600 mg/kg/day in the mouse). Consequently, it is considered that the NOAEL of 50 mg/kg/day identified in the rat multigeneration study is also likely to produce no adverse effects in mice for which there is only a LOAEL of 300 mg/kg/day (for a small but statistically significant decrease in epididymal weight in F_1 males only). Therefore, the NOAEL of 50 mg/kg/day identified from the multigeneration study will be used for risk characterisation purposes with respect to effects on fertility.

No evidence that bisphenol-A is a developmental toxicant was observed in standard development studies in rats and mice. In rats, a maternal LOAEL and foetal NOAEL of 160 and 640 mg/kg/day respectively, were identified (NTP 1985c; Morrisey et al 1987) . In mice, maternal and foetal NOAELs were 250 and 1000 mg/kg/day, respectively (NTP 1985a). In a rat multigeneration study, a statistically significant decrease in mean pup body weight gain, with concomitant delays in the acquisition of developmental landmarks (vaginal patency and preputial separation) was observed at 500 mg/kg on post-natal days 7-21 in males and females of all generations (F_1-F_3) (Tyl et al 2002). These decreases in pup body weight gain and delays in development

were seen in the presence of maternal toxicity. No maternal toxicity and no treatment-related effects were reported in the offspring of animals exposed to 50 mg/kg. However, additionally, some studies have investigated the potential of bisphenol-A to affect male reproductive tract development in rats and mice. Conflicting results have been reported in these studies in both species. In mice, adverse effects on male reproductive tract development (an increase in prostate weight in two studies and a reduction in epididymis weight in one study) have been reported at dose levels in the range 2 – 50 microgrammes/kg (Nagel et al 1997; vom Saal et al 1998; Gupta 2000). However, these results have not been reproducible in two other studies, one of which included additional dose levels, and using larger group sizes compared with those used in either of the two studies showing effects (Cagen et al 1999; Ashby et al 1999). Furthermore, no functional changes in reproductive parameters or reproductive organ development were observed in a recent rat two-generation study using similar dose levels (Chemical Compound Safety Research Institute 2000)_. The reasons for the differences in these results are unclear. Recent evidence from one study suggests that there are differences in the sensitivity of different mice strains to the effects of oestrogens, which may be related to the selection of strains for large litter size (Spearow et al 1999). This difference in sensitivity may in part explain some of the differences in the current database, although the relevance of these rodent strain differences in relation to human health remains unclear.

Overall, in standard developmental studies in rodents, there is no convincing evidence that bisphenol-A is a developmental toxicant. However, the available and apparently conflicting data from studies conducted using low doses (in the microgramme/kg range) do raise uncertainties.

Recommendation:

In relation to establishing a recommended occupational exposure limit (OEL), SCOEL began by considering the available data relating to inhalation exposure. In rats exposed daily to airborne bisphenol A for 13 weeks there was a clear NOAEL of 10 mg/m3, with mild olfactory epithelium inflammation at 50 and 150 mg/m3. There was no evidence of systemic toxicity in this study; if it is assumed that all of the inhaled bisphenol A was retained and absorbed, exposure to 150 mg/m3, a level at which no systemic effects were observed, would equate to a body burden in the rat of about 34 mg/kg/day.

If one then considers the surrounding toxicological evidence, most of which arises from oral dosing studies in rodents, there are no findings that preclude the recommendation of a health-based occupational exposure limit. Inlong-term repeated oral dosing studies NOAELs of 74 mg/kg/day in rats and 80 mg/kg/day in dogs have emerged; in mice, liver toxicity was seen at 120 mg/kg/day, the lowest dose level used. The use of these results to make predictions of dose-response characteristics for inhalation exposure, via route-to-route extrapolation, is hampered by the knowledge that following oral dosing there is extensive first-pass metabolism of bisphenol A absorbed and transported directly to the liver. Nevertheless, the available data from

oral dosing studies support the contention that no systemic toxicity arises in experimental animals with inhalation exposures in the region of 10 mg/m3.

Dramatically contrasting results have been reported in different laboratories conducting standard and non-standard developmental toxicity studies in rats and mice. This has been an area of much dispute, centred on the alleged endocrine-modulating potency of bisphenol A. Although further studies are being conducted in an attempt to clarify the situation, the judgement of SCOEL was to regard the 50 mg/kg/day NOAEL established in a standard multigeneration study in rats, as the most appropriate reference point for OEL considerations. Set against the analysis above, this suggests no concern for reproductive toxicity in experimental animals with exposures in the region of 10 mg/m^3.

Returning to the repeated inhalation NOAEL of 10 mg/m^3 in rats, with mild nasal olfactory epithelium inflammation arising at 50 mg/m^3, and considering extrapolation of these findings to humans, one would predict that humans could be less sensitive that rats to this effect, based on what is understood of general differences in inhaled particle deposition between the two species. SCOEL thereby arrived at a conclusion that repeated inhalation exposure to 10 mg/m3 bisphenol A (as inhalable dust) would pose no concern for local or systemic toxicity and therefore recommended an 8h TWA OEL at this level. In humans inhalaing 10 m3 of air, if it is assumed that all of the inhaled bisphenol A would be retained and absorbed (a worst-case assumption), this would result in a body burden of just a little over 1 mg/kg/day.

There is no toxicological basis for recommending an additional specific short-term OEL; nor are “Sk” or “Sen” notations appropriate.

An appropriate method is available to measure airborne bisphenol-A in relation to the occupational exposure limit recommended (NIOSH 1980).

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