Bisphenol A and its Diglycidylether

Health based recommended occupational exposure limits

GEZONDHEIDSRAAD
Voorzitter

Aan de minister van Volksgezondheid, Welzijn en Sport
Sir Winston Churchilllaan 370
2285 SJ RIJSWIJK

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Bij brief van 3 december 1993, nr. DGV/BMO-U-932542, verzocht de toenmalige staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de minister van Sociale Zaken en Werkgelegenheid om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

Per 1 januari 1994 heb ik daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door genoemde minister ingestelde adviescommissie.

Hierbij bied ik u - gehoord de Beraadsgroep Toxicologie - een publicatie van de Commissie WGD aan over 'Bisphenol-A and its Diglycidylether'.

prof dr JJ Sixma

Postadres
Postbus 1236
2280 CE Rijswijk
Telefoon (070) 340 75 20
Telefax (070) 340 75 23

Bezoekadres
Bogaard Centre
Sir Winston Churchilllaan 366-368
2285 SJ Rijswijk

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Report of the Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to

the Minister of Health, Welfare and Sports

the Minister and State Secretary of Social Affairs and Employment

No. 1996/02WGD, Rijswijk, 12 September 1996

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Samenvatting en advieswaarde

1 Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid beveelt de Gezondheidsraad gezondheidskundige advieswaarden aan voor beroepsmatige blootstelling aan toxische stoffen in de lucht op de werkplek. De aanbevelingen worden opgesteld door de Commissie WGD van de Raad. Zij vormen de eerste stap in een drietraps-procedure die moet leiden tot wettelijke grenswaarden (MAC-waarden).
In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan bisfenol A en bisfenol-A-diglycidylether en beveelt zij gezondheidskundige advieswaarden voor deze stoffen aan. De conclusies van de commissie zijn gebaseerd op de wetenschappelijke publikaties die vóór december 1995 zijn verschenen.

2 Fysische en chemische eigenschappen

Bisfenol A (BPA) komt voor in de vorm van witte kristallen of vlokken, heeft een zwakke fenol-achtige geur en een lage dampspanning. Verstoven BPA-poeder in lucht is explosief. BPA is in geringe mate oplosbaar in water, in tetrachloorkoolstof, en in verscheidene organische oplosmiddelen.

De diglycidylether van bisfenol A (DGEBPA) is in zuivere vorm een witte kristallijne stof en heeft een lage dampspanning. DGEBPA wordt niet als zuiver monomeer geproduceerd, maar als een mengsel van monomeer, dimeer, trimeer en tetrameer.

Over de fysische en chemische eigenschappen van de stof in zuivere vorm zijn maar weinig gegevens.

Beide verbindingen worden voornamelijk gebruikt bij de productie van harsen.

3 Monitoring

Het National Institute for Occupational Safety and Health (NIOSH) van de VS heeft een methode beschreven voor de bepaling van BPA en DGEBPA in lucht. Er is geen gevalideerde methode voor biologische monitoring beschikbaar.

4 Grenswaarden

Nederland, Duitsland, het Verenigd Koninkrijk, Zweden en de VS kennen geen grenswaarden voor beroepsmatige blootstelling aan de hier beschouwde stoffen.

5 Toxicokinetiek

Over de kinetiek van beide stoffen na inademing is niets bekend.

Bij ratten vindt na orale inname van BPA snel absorptie plaats. Binnen 3 dagen wordt ongeveer 80% uitgescheiden. Hetzelfde geldt voor DGEBPA bij muizen. Bij deze diersoort is de absorptie na dermale toediening veel langzamer dan na orale inname. Na drie dagen werd 41% van de aangebrachte dosis aangetroffen op de huid, 22 tot 30% op de bodemdeklaag van de kooi en 4,1% in het spoelwater na reiniging van de kooi. De fecale uitscheiding varieert met de dosis: van 10% bij een hoge tot 36% bij een lage dosis. De uitscheiding via de urine is veel geringer.

Het metabolisme van BPA is niet onderzocht. Bij muizen zijn de metaboliet-patronen in urine en feces na toediening via de huid in essentie dezelfde als die na orale toediening. De belangrijkste metaboliet in de urine is bis-diol-DGEBPA, gevolgd door het sulfaat-conjugaat gaat hiervan. Het belangrijkste fecale metaboliet is de aan een kant tot carboxylzuur geoxideerde bis-diol-verbinding.

6 Effecten

BPA

BPA is licht irriterend voor de huid, maar maakt de huid niet overgevoelig. De acute toxiciteit is laag. Subchronische blootstelling aan concentraties van 50 en 150 mg/m^3, hetgeen bijna de maximaal haalbare concentratie in lucht is, veroorzaakte bij ratten

lichte hyperplasie en chronische ontsteking in de neusholte. Deze effecten verdwenen binnen 12 weken na beëindiging van de blootstelling. De geen-waargenomen-nadelig-effect-concentratie bij 90 dagen van blootstelling was 10 mg/m^3. Langdurige orale blootstelling leidde bij ratten tot vermindering van groei en vervolgens tot toxische effecten in lever en nieren. Er zijn geen aanwijzingen dat BPA carcinogeen is voor ratten of muizen van beide seksen. Ook is niet gebleken dat BPA bij ratten en muizen genotoxiciteit vertoont, evenmin als reproductie- en ontwikkelingstoxiciteit.

Bij de mens veroorzaakt BPA lichte irritatie van de huid, de ogen, de neus en de keel. Allergische reacties zijn echter, ook bij geselecteerde groepen van industriële werkers, slechts bij hoge uitzondering waargenomen.

DGEBPA

DGEBPA irriteert de huid en maakt deze sterk overgevoelig. De acute toxiciteit is gering. Orale toediening van een dosis van 540 mg/kg per dag aan mannelijke ratten gedurende 10 weken leidde tot vermindering van het lichaamsgewicht, maar niet tot macroscopische veranderingen, effecten op orgaangewichten of histologische veranderingen in de voortplantingsorganen of het spijsverteringskanaal. Bij mannelijke en vrouwelijke muizen is geen carcinogeniteit gebleken na toediening via de huid of subcutane injecties. De stof heeft enige mutagene activiteit, maar deze is hoofdzakelijk waargenomen in *in vitro*-experimenten. Verscheidene *in vivo*-experimenten hebben, evenmin als onderzoek met humane cellen *in vitro*, geen aanwijzingen voor genotoxiciteit opgeleverd. Doses die voor het moederdier toxisch waren (540 mg/kg/dag bij ratten, 180 mg/kg/dag bij konijnen), leidden niet tot reproductietoxische effecten of ontwikkelingsstoornissen. De geen-waargenomen-nadelig-effectniveaus voor de hier bedoelde maternale toxiciteit waren 180 mg/kg/dag voor ratten en 60 mg/kg/dag voor konijnen.

De incidentie van huid-overgevoeligheid bij mensen is ongeveer 4%. In enkele gevallen kan DGEBPA astma veroorzaken.

7 Evaluatie en advieswaarden

BPA

Het kritische effect is de zeer lichte tot lichte nasale hyperplasie en ontsteking, bij 50 en 150 mg/m^3, zoals waargenomen bij inhalatie-experimenten met ratten en die volledig verdwenen binnen 12 weken na beëindiging van de blootstelling. Het geen-waargenomen-nadelig-effectniveau was 10 mg/m^3. Voor de extrapolatie van rat naar mens vindt de commissie het gebruik van een veiligheidsfactor niet nodig. Systemische

effecten zijn immers niet waargenomen en bovendien bedraagt de marge tussen het geen-waargenomen-effectniveau en het laagst-waargenomen-effectniveau een factor 5. Wegens de lage dampspanning kan een concentratie van 10 mg BPA per m^3 lucht slechts bestaan in de vorm van vaste deeltjes.

DGEBPA

De kritische effecten zijn de vermindering van het lichaamsgewicht na orale toediening aan mannelijke ratten en maternale toxiciteit bij zwangere konijnen. De commissie neemt als uitgangspunt het geen-waargenomen-nadelig-effectniveau van 60 mg/kg/dag in konijnen. Voor extrapolatie van konijn naar mens hanteert de commissie als veiligheidsfactor 10. De hieruit onder bepaalde aannamen af te leiden gezondheidskundige advieswaarde bedraagt ongeveer 40 mg DGEBPA per m^3 lucht.. Wegens de lage dampspanning van DGEBPA kan deze concentratie in lucht uitsluitend bestaan in de vorm van vaste deeltjes.

Beide stoffen komen in de lucht op de werkplek vermoedelijk uitsluitend voor in de vorm van stofdeeltjes. De hierboven afgeleide gezondheidskundige advieswaarden zijn in geval van BPA gelijk aan en in geval van DGEBPA hoger dan de in Nederland geldende MAC-waarde voor stofdeeltjes. De commissie stelt daarom voor om, gemiddeld over een acht-urige werkdag, de concentratie van respirabel respectievelijk inhaleerbaar BPA en DGEBPA in de lucht op de werkplek te beperken tot 5 respectievelijk 10 mg/m^3, gemiddeld over een acht-urige werkdag.

Ter voorkoming van huid-overgevoeligheid dient huidcontact met DGEBPA te worden vermeden.

Executive summary

1 Scope

Upon request of the Secretary of State of Social Affairs and Employment the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in the air of the workplace. These recommendation are made by the Council's Dutch Expert Committee on Occupational Standards. It constitutes the first step in a three-stage procedure that leads to legally binding limit values. In the present report the Committee discusses the consequences of exposure to bisphenol A and bisphenol-A-diglycidylether and recommends health-based occupational exposure limits for these substances. The Committee's conclusions are based on scientific publications obtained from data retrieval systems from prior to December 1995.

2 Physical and chemical properties

Bisphenol A (BPA) consists of white crystals or flakes and has a mild phenolic odour. Finely dispersed powder with air is explosive. The substance is slightly soluble in water and CCl_4, and soluble in several organic solvents.

The pure diglycidylether of bisphenol A (DGEBPA) is a white crystalline solid. DGEBPA is not produced as a pure monomer but as a mixture of monomer, dimer, trimer and tetramer, and, therefore, very few chemical and physical properties are reported for the pure substance. Both BPA and DGEBPA have a low vapour pressure.

3 Monitoring

The National Institute for Occupational Safety and Health (NIOSH) of the USA has described a method for measurement of BPA and DGEBPA in air, based on sampling of particulates, extraction, and analysis on an HPLC equipped with uv detection. There is no validated method for biological monitoring.

4 Limit values

No occupational exposure limits for these substances have been set in the Netherlands, Germany, UK, Sweden and the USA.

5 Toxicokinetics

There is no information on the kinetics of both compounds after inhalation exposure.

Absorption of BPA after oral dosing to rats is rapid. Within 3 days approximately 80% is excreted. The same holds for DGEBPA after oral dosing to mice.

Absorption of DGEBPA after dermal application to mice is much slower. After three days of exposure 41% of the dose is recovered from the skin, 22 - 30% from the foil covering and 4.1 % from the cage washing. Faecal excretion varies with the dose and ranges from 10% for a high dose to 36% for a low dose. Urinary excretion is much less.

The metabolism of BPA has not been studied. In mice the urinary and faecal metabolite profiles of DGEBPA after dermal and oral administration are essentially the same. The main urinary metabolite is bis-diol-DGEBPA, followed by the sulfate conjugate of bis-diol-DGEBPA. The main faecal metabolite is the bis-diol-compound oxidized at one end to a carboxylic acid.

6 Effects

BPA

BPA is a slight skin irritant, but not a skin sensitizer. It has a low acute toxicity. Subchronic inhalation exposure to 50 mg/m^3 and 150 mg/m^3 which is almost the maximum attainable concentration in air, induced very slight to slight hyperplasia and chronic inflammation in the nasal cavity of rats. The effects were reversible upon cessation of exposure. The 90-day no-observed-adverse-effect level was 10 mg/m^3. Long-term oral

dosing reduces the weight gain, followed by toxicity in liver and kidney. There is no evidence that BPA is carcinogenic for rats or mice of either sex. BPA has no mutagenic or genotoxic activity. BPA does not induce reproductive or developmental toxicity in rats and mice.

In humans BPA induced mild irritation in skin, eyes, nose and throat. Even in selected groups of workers allergic reactions to BPA are only elicited in rare cases.

DGEBPA

DGEBPA is a skin irritant and a strong skin sensitizer. It has low acute toxicity. Ten weeks of oral dosing of 540 mg/kg per day to male rats reduced the body weight but did not induce macroscopic changes, organ weights changes or histologic changes in the reproductive or alimentary tract. DGEBPA was not carcinogenic in male and female mice after dermal application and sc injections. The substance has some mutagenic activity, but mainly in *in vitro* studies. Several *in vivo* studies and in human cells *in vitro* revealed no genotoxicity. DGEBPA did not induce reproductive or developmental toxicity in rats, rabbits and mice at dosages which induce maternal toxicity (540 mg/kg per day for rats, 180 mg/kg per day for rabbits). The no-observed-adverse-effect levels were 180 mg/kg/day for rats and 60 mg/kg/day for rabbits.

DGEBPA is a skin sensitizer for humans. The incidence in occupationally exposed workers is approximately 4%.

7 Recommended occupational exposure limits

BPA

The critical effect which was found in an inhalation study with intermittent exposure with rats was the slight to very slight nasal hyperplasia and inflammation at 50 and 150 mg/m^3. This effect was fully reversible within 12 weeks after cessation of exposure. The NOAEL was 10 mg/m^3. To extrapolate from rat to man a safety factor is not considered necessary because of the absence of systemic effects, and the fact that the margin of safety between the NOAEL and the LOAEL for local effects is a factor 5. Due to the low vapour pressure of BPA 10 mg/m^3 can only be present in the air as solid particles.

DGEBPA

The critical effects were the reduced body weight that was observed in several studies with oral dosing to male rats and maternal toxicity in pregnant rabbits. The committee

takes the NOAEL of 60 mg/kg/day in rabbits as a starting point for the evaluation. To extrapolate from rabbit to man a safety factor of 10 is used. The calculated corresponding concentration in air is about 40 mg/m^3. Due to the expected low vapour pressure of DGEBPA this concentration can only be present in air as solid particles.

Both substances are expected to occur only as particulate matter in the occupational situation. The calculated health-based recommended occupational exposure limits are equal to (BPA) or exceed (DGEBPA) the Maximum Allowed Condentration for particle dusts in the Netherlands. DECOS recommends an occupational exposure limit of 5 mg/m^3 for respirable BPA and DGEBPA and of 10 mg/m^3 for the compounds in inhalable form, to be averaged over an 8 hour workday (8-h TWA). These limits are equal to the Maximum Allowed Concentrations for particle dusts in the Netherlands.

In order to prevent sensitization skin contact with DGEBPA should be avoided.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the minister of Social Affairs and Employment (annex A). The purpose of the committee's evaluation is to set a health-based recommended exposure limit for the atmospheric concentration of the substance. Such an exposure limit cannot be set if insufficient data is available or if the toxic action of the substance cannot be evaluated using a threshold model.

In the next phase of the three-step procedure, the Social and Economic Council advises the minister on the feasibility of using the health-based limit as a regulatory Maximum Accepted Concentration (MAC) or recommends a different MAC. In the final step of the procedure, the Minister of Social Affairs and Employment sets the official exposure limit.

1.2 Committee and procedures

The present document contains the assessment of DECOS, hereafter called the committee, of the health hazard of Bisphenol A and its Diglycidylether. The members of the committee are listed in annex B. The first draft of this report was prepared by drs

MA Maclaine Pont, from the Wageningen Agricultural University, by contract with the Ministry of Social Affairs and Employment.

In 1994/1995 the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The literature was obtained from data retrieval systems up to December 1995.

Chapter 2

Identity, properties, monitoring

2.1 Identity

2.1.1 Structure

Bisphenol A (BPA) consists of white crystals or flakes and has a mild phenolic odour (Lew92; Win76; NIA92).

2.1.2 Chemical names and synonyms/registry number

The Chemical Abstracts Service registry number (CAS reg. nr.) is *80-05-7*. The chemical substance prime name of BPA used by the Service is *4,4'-(1-methylethylidene)bisphenol*, synonyms are listed in annex D.

The pure diglycidylether of bisphenol A (DGEBPA) is a white crystalline solid (De Jong, personal communication). The typical commercial unmodified resins are viscous liquids with a viscosity of 11-16 Pa s at 25 °C (Kir80). However, older data report that DGEBPA is a light yellow epoxy resin with a viscosity from 9 to 13 Pa s and an epoxide content of ca. 5.1 equivalents/kg (Ull75). Furthermore, it is reported that DGEBPA is a yellowish brown odourless liquid (Ano93).

The CAS reg. nr. is *1675-54-3*. The chemical substance prime name of DGEBPA used by the Service is *2,2'-((1-methylethylidene)bis-(4,1-phenyleneoxymethylene))bisoxirane*, synonyms are listed in annex E.

2.1.3 *Physical and chemical properties (CEC/IPCS, 1991)*

Physical and chemical properties of BPA are listed in Table 1 and of DGEBPA in Table 2.

DGEBPA is not produced as a pure monomer but as a mixture of monomer, dimer, trimer and tetramer; therefore very few chemical and physical properties are reported for the pure substance (IAR89).

2.2 Analytical methods

Environmental monitoring

A method of the National Institute for Occupational Safety and Health (NIOSH) is available. The method is based on sampling of BPA and DGEBPA as a particulate from the air on a filter, extraction with acetonitrile and analysis with reversed phase high performance liquid chromatography (HPLC) and ultraviolet detection at 230 nm.

Table 1 Physical and chemical properties of BPA.

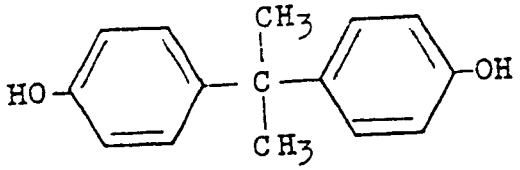
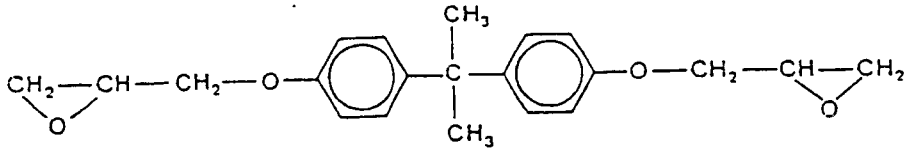
molecular formula	$C_{15}H_{16}O_2$
structural formula	
molecular weight	228.29
melting point	152-3 °C (Lid92); 153 °C (NIA92); 157 °C (Oom83)
vapour pressure	0.027 kPa at 170 °C (Dor87; BIB89)
flash point	207 °C (NIA92); 227 °C (Ull79) [cup?]; 79.4 °C Tag open cup (Ano67
explosion	finely dispersed powder with air is explosive (NIA92)
autoignition temperature	600 °C (NIA92)
density	1.04 g/cm^3 at 20 °C (Ull79) 1.195 (25/25 °C; Ano67)
solubility; in water:	at 25 °C: < 100 - 120 mg/100 mg;
in alcohol:	at 83 °C: 344 mg/100 g;
in CCl_4:	soluble;
in ether, benzene, acetic acid, acetone, methanol:	slightly soluble; soluble (Ano67; Win76; Ull79; Dor87; Lid92; Lew92)
log P_{oct}	2.20 (Dor87); 4.0917 (McC90)

Table 2 Physical and chemical properties of DGEBPA

molecular formula	$C_{21}H_{24}O_4$
structural formula	
molecular weight	340.42
melting point	8-12 °C (Hin81); 43 °C (Kir80)
flash point Epikote 828[a]	> 150 °C (Web93)
density Epikote 828	1160 kg/m^3 at 25 °C (Web93)

[a] A mixture of oligomers, mainly consisting of DGEBPA, with a MW of 350 - 380 (Web93).

The working range is 0.441 - 1.77 mg/m^3 BPA and 0.441 - 1.78 mg/m^3 DGEBPA based on a 288 l air sample. Any compound which has the same retention time as either BPA or DGEBPA, under the operating conditions of this method, may interfere (NIO80).

Oomens and Schuurhuis (Oom83) improved this method. In their method air samples are concentrated on commercial silica, desorbed with a mixture of methanol and water (60:40 v/v) and analyzed by HPLC, using UV detection at 275 nm. This method has been validated for a concentration range of 0.5-50 mg/m^3 BPA based on a 10 l air sample.

Biological monitoring

No validated method is available. An analytical method for biological monitoring has been developed by Eadsforth (Ead83), see Chapter 5.5.

Chapter 3

Sources

3.1 Natural occurrence

BPA and DGEBPA are not known to occur as natural products.

3.2 Man-made sources

3.2.1 Production

BPA is manufactured by condensation of phenol with acetone under acidic conditions. In 1978 production of BPA in the United States was approximately 160 000 tons per year (Kir78). The estimated average annual USA production of BPA for 1980 was 530 million pounds and was projected to increase to meet an estimated annual demand of 770 million pounds (Mor87). In the second half of the seventies in Western Europe the amount of BPA used in a year is 136 000 tons (Ull79). In 1991 the Dutch capacity to produce BPA was 170 000 tons. Within the EC a quantity of 310 000 tons was produced in 1989 (ECD93).

DGEBPA is synthesized from BPA and epichlorohydrin. Epoxy resins can be made by reaction of DGEBPA and BPA (Ull75). Epoxy resins usually consist of DGEBPA (MW 340) (Hol93) and several oligomers of MW 624, 908, 1,192, 1,476 etc. (Tho78). Low molecular weight resins (average MW <1000) contain up to 95% DGEBPA and high-molecular weight resins (average MW >1000) contain from traces to 10% DGE-

BPA (Fre81). Other components, known as hardeners are added to the system to facilitate polymerization. Common types of hardeners include amines (diethylenetriamine, triethylenetetramine and 4,4'-diaminophenylmethane) and acid anhydrides (phthalic anhydride) (Hol93). When hardened at room temperature 5 - 25% remains unhardend for months; high temperatures usually give complete hardening (Mor87). Reactive diluents may also be added, such as n-butyl glycidyl ether, cresyl glycidyl ether, phenyl glycidyl ether and Epoxide-8 (Hol93). Epoxy resins are products of considerable commercial significance with a production of 143,000 metric tons (315 million pounds) in 1980 in the USA (Her87).

No European data are available on capacity, production or consumption (EC93).

3.2.2 *Uses*

The most important application of BPA is the manufacturing of epoxy, polycarbonate and corrosion resistant unsaturated polyester-styrene resins (Ull79; Kir78). BPA is also used as an antioxidant (Ull79), as a fungicide (Win76), and as antimicrobial substance in cosmetics (Mat83).

In the EC about 50% is used for polycarbonate resins and about 40% for epoxy resins (ECD93).

About 75 to 90% of the epoxy resins in industrial use are of the diglycidylether bisphenol-A-type (Tos92).

Approximately 45% of the total production of epoxy resin is used in protective coatings (Her87). Flyvholm (Fly91) mentioned uses of DGEBPA in a broad spectrum of products. Of 1291 products containing DGEBPA 563 were used as paints and lacquers, 217 as binders, 104 as hardeners, 96 as adhesives, and 94 as fillings. Minor applications are castings (69), flooring materials (49), printing inks (35), construction material (31), metal coatings (17), corrosion inhibitors (11), and colouring agents (5). DGEBPA is widely used in the home environment; unhardened epoxy resin oligomer with a MW of 340 has been demonstrated in hobby glues, on signboards, capsules of bottles, twist-off covers, film cassettes, metal packages and brass door knobs (Fre80). Resins, which still might contain BPA or DGEBPA, have found applications as low pressure moulding mixtures and binding agents for fiber glass products, electrical moulding powders and decorative or industrial powder coatings. Uncured they are used as plasticizers and stabilizer for vinyl resins (Hin81). Resins are also used in interior coatings of cans and drums, reinforced pipes, watermain filters, nail polish, food packaging materials (Mor87) and ski sticks (Suh83).

Chapter 4

Exposure

4.1 Environmental levels

4.1.1 Water

The highest concentration of BPA expected in effluent was reported to be 0.08 mg/l by Shell and no greater than 0.1 mg/l on the average by other companies (Dor87).

DGEBPA is reported to be found in drinking water in the UK, where epoxy resin was used for lining cast-iron water pipes to inhibit corrosion of existing water distribution systems. All compounds reported in this study were present at the low micrograms per litre concentration range or less (Cra84).

4.1.2 Food

Neither compound occurs naturally in food. Nevertheless, migration can occur from cans or other packaging material, where the compounds are used in coatings.

From cans with preserved food weighing 300 - 450 g 4 - 23 µg BPA/can could be extracted (Bro95).

Migration of BPA from three different epoxy resins, used as coating material in wine-butts, to several wine-simulants has been studied (Lar89). The amount of BPA released from the resins is stimulated by low pH and high alcoholic strength, but never

exceeds 97 mg BPA/kg resin. This corresponds with 0.65 mg/l if a wine-butt of 15 hl is coated with 10 kg resin.

Migration tests have been carried out using cans coated with a commercial heat-cured lacquer formulation containing less than 0.001 mg DGEBPA per can. Using a food simulant the detection limit was 0.01 mg/kg, and the half-life of DGEBPA in the food simulant was less than two days at 40 C. Food containers that were cold-cured contained more monomer residues (DGEBPA) [not quantified], but no DGEBPA was detected in migration tests with the food simulants, using the same test-conditions (Tic88).

DGEBPA, used in an acrylic/epoxy adhesive, migrates through poly(ethylene terephthalate) film into a food simulating liquid (FSL) and into food under microwave susceptor cooking conditions. The FSL is a fractionated coconut oil and the food used in this experiment was a commercial meat-and-vegetable-filled pastry product designed for microwave susceptor cooking. The average DGEBPA migration values were 1.33 and 8.59 µg/g for food and FSL respectively, corresponding to a migration on a surface area basis of 1.26 and 5.67 µg/cm^2. This susceptor package does not meet the requirements of the United States and European Community regulations (section 4.1). The company no longer uses the adhesive, containing DGEBPA, in its microwave susceptor packaging anymore (Beg91).

4.1.3 Air (ambient)

No data available.

4.2 Human exposure

4.2.1 General population

No data available.

4.2.2 Occupational population

Most of the human exposure to BPA occurs in industry during the manufacture of resins (Fre81).

NIOSH estimated in 1979 that approximately 200,000 individuals were exposed to BPA during resin manufacturing or formulation (Mor87), and 45,700 and 13,138 workers were potentially exposed to DGEBPA in the USA in 1972-1974 and 1981-1983, respectively (IAR89). During use of a powder spray paint, levels of DGE-

BPA ranged from 0.005 to 0.200 mg/m^3 in personal samples and from 0.002 to 0.008 mg/m^3 in area samples (IAR89).

There were no detectable (detection limit ranges from 0.02 to 0.1 µg/ml) residues of DGEBPA in urine samples from workers at a plant making epoxy resins, suggesting minimal exposure, if any, to DGEBPA (Ead83). No data were given on exposure levels.

Chapter 5

Guidelines and standards

5.1 General population

The USA Food and Drug Administration permits the use of epoxy resins as components of coatings that may come into contact with food (IAR89). The current regulations specify the presence of a functional barrier between the adhesive components and the food (Beg91).

The Tolerable Daily Intake for man of BPA estimated by the EC Scientific Committee for Food was 0.05 mg/kg bw (BIB89).

The European Community allows up to a maximum of 0.02 μg DGEBPA per gram food or food simulating liquid (Beg90).

5.2 Working population

5.2.1 Occupational exposure limits

No exposure limits have been set for BPA and DGEBPA in The Netherlands, Germany, UK, Sweden and the USA.

In 1962 5 mg/m^3 was recommended by Russian sources as the maximum allowable concentration in air for manufacturing installations. In 1964 it was again recommended (Ano67).

The Federal Government of the USA limited worker exposure to BPA to a ceiling concentration of 2.8 mg/m^3 of air in 1974 (cited in Geo85). The Dow Chemical Company is using an industrial hygiene guideline of 5 mg/m^3 8 h time-weighted average (TWA) for BPA (respirable or inhalable?) (Oom83).

In Denmark, Norway, and Finland DGEBPA must be labeled with risk phrase R43: may cause sensitization by skin contact (Fly91).

5.2.2 *Biological exposure indices*

No exposure limits have been set for BPA and DGEBPA.

5.3 Previous evaluation by national and international bodies

The International Agency for Research on Cancer (IARC) reviewed available data with emphasis on carcinogenicity and mutagenicity. It concluded that there is limited evidence for the carcinogenicity of DGEBPA in experimental animals, but that DGEBPA is not classifiable as to its carcinogenicity to humans (group 3) (IAR89).

Chapter 6

Kinetics

6.1 Absorption

The metabolism of BPA was studied (Kna66). Groups of four male rats (Carworth Farms, Elias Stock) were dosed once orally with a mixture of 120 mg of labeled and non-labeled BPA. The daily urine and faecal samples were pooled and collected for a period of eight days, whereupon the animals were sacrificed. Over the eight-day period 28% of the ^{14}C was excreted in the urine and 56% in the faeces (Figure 1). No ^{14}C could be detected in exhaled CO_2, and at the end of eight days no ^{14}C residues could be detected in the carcass. A crude estimate of the elimination half life time in rats is a little bit more than 1 day.

The authors tried to identify metabolites, but their methods of analysis had problems: the glucuronide was found to be extremely resistent to acid hydrolysis, the mammalian ß-glucuronidase preparations varied in their activity and the products extracted from faeces could not be analyzed under the GLC conditions used. Moreover, a possible hydroxylated metabolite was found, but the only attempt to confirm the structure was by means of acetylation of the product, followed by comparison with BPA-diacetate. Both compounds had the same retention time upon GLC analysis, indicating that the compounds were probably identical. Based upon the weaknesses in the analytical procedure, it is concluded that the only valid data in this study are the radioactivity profiles as presented in the first paragraph (Kna66).

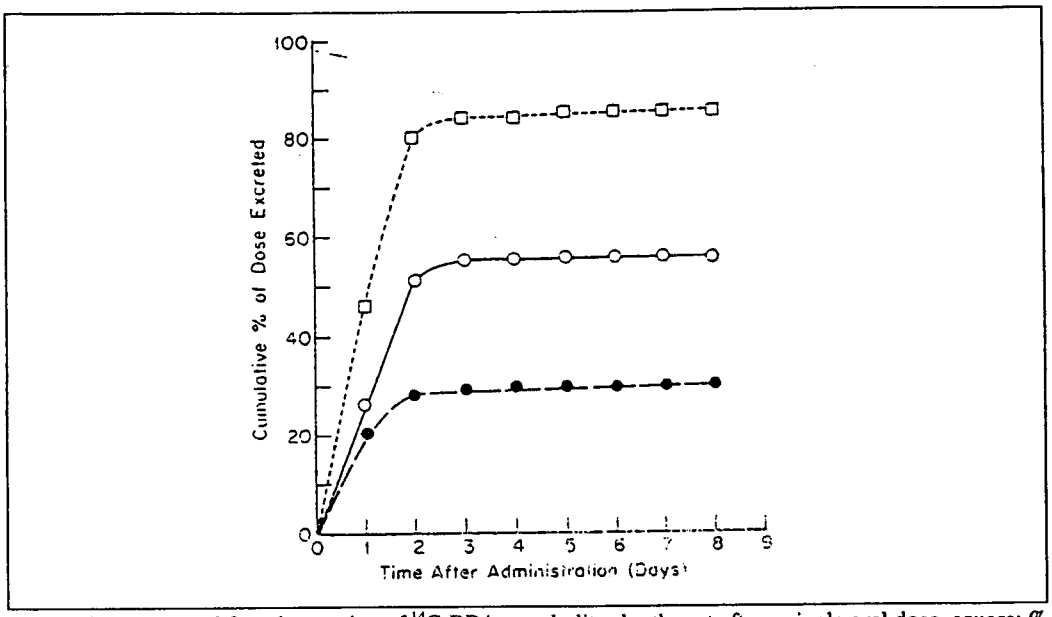


Figure 1 Urinary and faecal excretion of ^{14}C-BPA metabolites by the rat after a single oral dose. square: % in urine and faeces; open circles: % in faeces; closed circles: % in urine (Kna66).

When ^{14}C-DGEBPA was given orally to six male CF1 mice (approximately 55 mg/kg body weight), it was rapidly excreted, 80% of the administered ^{14}C was eliminated in the faeces and 11% in the urine 0-3 days after a single oral dose (Cli81a).

When 1.6 mg ^{14}C-DGEBPA/mouse was dermally applied to six male CF1 mice (approximately 56 mg/kg body weight), followed by occlusive exposure for 1, 3 or 8 days, 20% of the dose was eliminated in faeces and 3% in urine, as a mixture of metabolites, over a period of three days. After three days of exposure 41% of the dose was recovered from the skin, 22 - 30% from the foil covering and 4.1% from the cage washing. After 8 days of exposure 36% of the dose was excreted via the faeces, 5.4% via the urine, 11% remained on the skin. The quantity recovered from the foil remained approximately constant throughout the experiment (Cli81a).

Radioactivity of topically applied centrally labeled DGEBPA was found in faeces and urine of C57BL6 mice [sex unknown], whereas DGEBPA labeled in the side-chain was excreted via faeces, urine and CO_2 (Table 3). After evaporation of the solvent the application site was occluded (Ben89).

Conclusion

No information on absorption after inhalation exposure was found.

Absorption of BPA after oral dosing to rats is rapid. Within three days ± 80% is excreted.

Table 3 Excretion of radioactivity 48 h after occlusive dermal application of 14C-DGEBPA to C57BL6 mice (Ben89).

DGEBPA I[a]	DGEBPA II[b]	percent of dose				n
mg/mouse	mg/mouse	faeces	urine	CO_2	application site	
0.4	-	35.3 ± 15.3	8.7 ± 2.6	0.5 ± 0.3	15.4 ± 8.8	5
2	-	10.6 ± 1.1	2.9 ± 0.1	0.2 ± 0.02	27.6 ± 10	2
-	0.4	36.3 ± 5.2	5.7 ± 1.9	-	9.9 ± 2.7	5
-	1.3	16.3 ± 0.2	6.4 ± 3.7	-	17.5 ± 1.0	2

[a] DGEBPA I is side chain labelled.

[b] DGEBPA II is centrally labelled.

Absorption of DGEBPA after oral dosing to mice is also rapid. Within three days ± 80% is excreted.

Excretion of DGEBPA after occlusive dermal application to mice depends on the dose and the time period. After 2 days of exposure to 0.4 mg/mouse faecal excretion amounted to 35 - 36% of the dose, whereas a quantity of 2 mg/mouse was excreted for ±10%. Three days after exposure to 1.6 mg/mouse the total faecal excretion amounted to ±20%. Urinary excretion is much less.

6.2 Distribution

The distribution of the radioactivity of ^{14}C-DGEBPA was investigated (Cli81a). The radioactivity in the tissues of six male CF1 mice after dermal application of ^{14}C-DGEBPA (approximately 56 mg/kg body weight) one, three and eight days after dosing is shown in Table 4. The mean total recovery was 94.8%. When ^{14}C-DGEBPA was dosed orally to six male CF1 mice (approximately 55 mg/kg) the tissue radioactivity rapidly depleted from all the tissues studied during the course of the eight day experiment (Table 5). The mean total recovery was 92.6% (we calculated 92.7%).

There are route-dependent differences in plasma ^{14}C concentration-time profiles, tissue/plasma ^{14}C ratios and urinary excretion following intravenous or oral administration of ^{14}C-DGEBPA to rats. The ^{14}C-DGEBPA was labeled at the isopropylidine methylene carbon. The plasma radioactivity that resulted from the oral administration of ^{14}C-DGEBPA was eliminated more rapidly than the radioactivity resulting from intravenous administration (study from 1981, reported by Gar92).

Conclusion

No data on distribution are available after inhalation exposure. In mice the distribution of DGEBPA after dermal and oral administration is essentially the same. Concentrations of less than 1% are found in all organs, in blood and in the remaining carcass. Af-

Table 4 Total recovery of radioactivity from male CF1 mice after dermal application of 14C-DGEBPA. Results are expressed as percentage of administered radioactivity (Cli81a).

day (mouse nr.)	1 (1)	1 (5)	3 (2)	3 (3)	8 (4)	8 (6)
urine	0.9	0.43	3.80	3.02	4.37	5.59
faeces	3.4	2.37	17.9	12.2	40.9	40.9
skin in toto	65.2	68.9	36.9	44.5	9.4	15.4
intestine	2.60	1.70	1.81	4.82	0.23	0.87
liver	0.2	0.23	0.3	0.51	0.05	0.06
kidney	0.03	0.04	0.04	0.07	<0.01	<0.01
blood	0.05	0.07	0.05	0.17	<0.01	0.02
remaining carcass	0.26	0.49	0.34	0.94	0.09	0.15
cage washing	2.2	0.6	4.11	4.42	3.3	5.8
foil covering	22.6	24.1	30.3	21.8	32.5	25.5
total	97.4	98.9	95.5	92.4	90.8	94

ter oral dosing the compound is mainly eliminated via the faeces. Eight days after dermal application a quantity of 9 - 15% remained on the total skin and 26 - 36% was found on the foil covering.

6.3 Biotransformation

Climie *et al* (Cli81a) showed that the urinary and faecal metabolite profiles derived from dermal application and oral dosage of DGEBPA were essentially similar. In a further study (Cli81b) the metabolic products of DGEBPA and their routes of formation are described, as they are found in male CF1 or CD1 mice.

One day after a single oral dose of ± 715 mg/kg approximately 0.1% of the dose was excreted via urine unchanged. At lower doses DGEBPA could not be detected. The main metabolite excreted in the urine was bis-diol-DGEBPA (4% of the dose), fol-

Table 5 Total recovery of radioactivity from male CF1 mice after oral dosage of 14C-DGEBPA. Results are expressed as percentage of administered radioactivity (Cli81a).

day (mouse nr.)	1 (1)	1 (2)	3 (5)	3 (6)	8 (3)	8 (4)
urine	8.8	12	13.5	9.32	9.46	9.93
faeces	80.4	53.7	67.7	81.2	82.2	78.9
skin in toto	0.2	0.36	0.12	0.11	0.07	0.06
intestine	2.7	28.3	0.14	0.19	0.01	0.01
liver	0.25	0.66	0.06	0.04	0.01	0.01
kidney	0.01	0.05	0.01	0.01	«0.01	«0.01
blood	0.02	0.15	0.01	0.01	0.01	0.02
remaining carcass	0.28	0.75	0.03	0.06	0.02	0.01
cage washing	0.77	0.99	3.06	2.76	3.4	3.49
total	93.4	97	84.6	93.7	95.2	92.4

lowed by the sulphate conjugate of bis-diol-DGEBPA (2% of the dose). One percent of the administered dose was excreted in the urine as phenol-diol-DGEBPA, and 1% as the glucuronide conjugate of phenol-diol-DGEBPA. No BPA could be detected.

In the faecal fraction a quantity of «0.1% of the dose chromatographed to the same R_f position as BPA. However, since this fraction was present in such small quantities no further work was performed. The presence of unchanged DGEBPA is not mentioned. Bis-diol-DGEBPA oxidized at one side to a carboxylic acid (compound VIIIa in Figure 2) was the main metabolite, it comprised 24% of the dose. The compound is also excreted as its glucuronide conjugate, comprising 3% of the dose. A further decarboxylation product (compound VIa) accounted for 14% of the dose. Its glucuronide conjugate was found in the faeces in a concentration of 1% of the dose. Other major compounds excreted in the faeces are compound Va (5%) and VIIa (4%). Phenol-diol-DGEBPA (3%) and bis-diol-DGEBPA (2%) are also excreted in the faeces.

A summary of the known and possible metabolic routes is given in figure 2. It can be concluded that the major metabolic transformation of orally ingested ^{14}C-DGEBPA is by hydrolytic ring-opening of the two epoxide rings to form diols. This metabolite (bis-diol-DGEBPA) is excreted in both free and conjugated forms and is further metabolized to various carboxylic acids, including two containing a methylsulphonyl moiety. The product of oxidative dealkylation either of DGEBPA (with concomitant formation of glycidaldehyde) or bis-diol-DGEBPA (with concomitant formation of glyceraldehyde) is excreted in both free and conjugated forms representing 5% of the dose.

In order to confirm that bis-diol-DGEBPA is a substrate for oxidative dealkylating enzymes it was fed to two mice. After a single oral dose of bis-diol-DGEBPA the total amount excreted was 9% of the dose via the urine (after one day) and 81% of the dose via faeces (after two days). The compound was excreted unchanged (5% of the dose in the urine and 5% in the faeces) or as a sulphate conjugate (2.5% of the dose in the urine). Another metabolite was also excreted: phenol-diol-DGEBPA (2% of the dose in the urine and 0.6% in the faeces) or as a glucuronide (0.4% of the dose via the urine). These two compounds were also excreted after administration of DGEBPA, in approximately the same amounts, indicating that the metabolic route of DGEBPA is via the bis-diol metabolite. In both excreta no BPA was detected.

Since epoxide ring opening is such an important metabolic pathway, the total hepatic DGEBPA epoxide hydratases of rat, mouse and rabbit were compared and found to be present in the ratio 1:2:3 (Cli81b). Data on human hepatic epoxide hydratases are not available.

A further dose-excretion study of DGEBPA has been carried out with rabbits, which have excretion characteristics more similar to those of man. The total amount of bis-

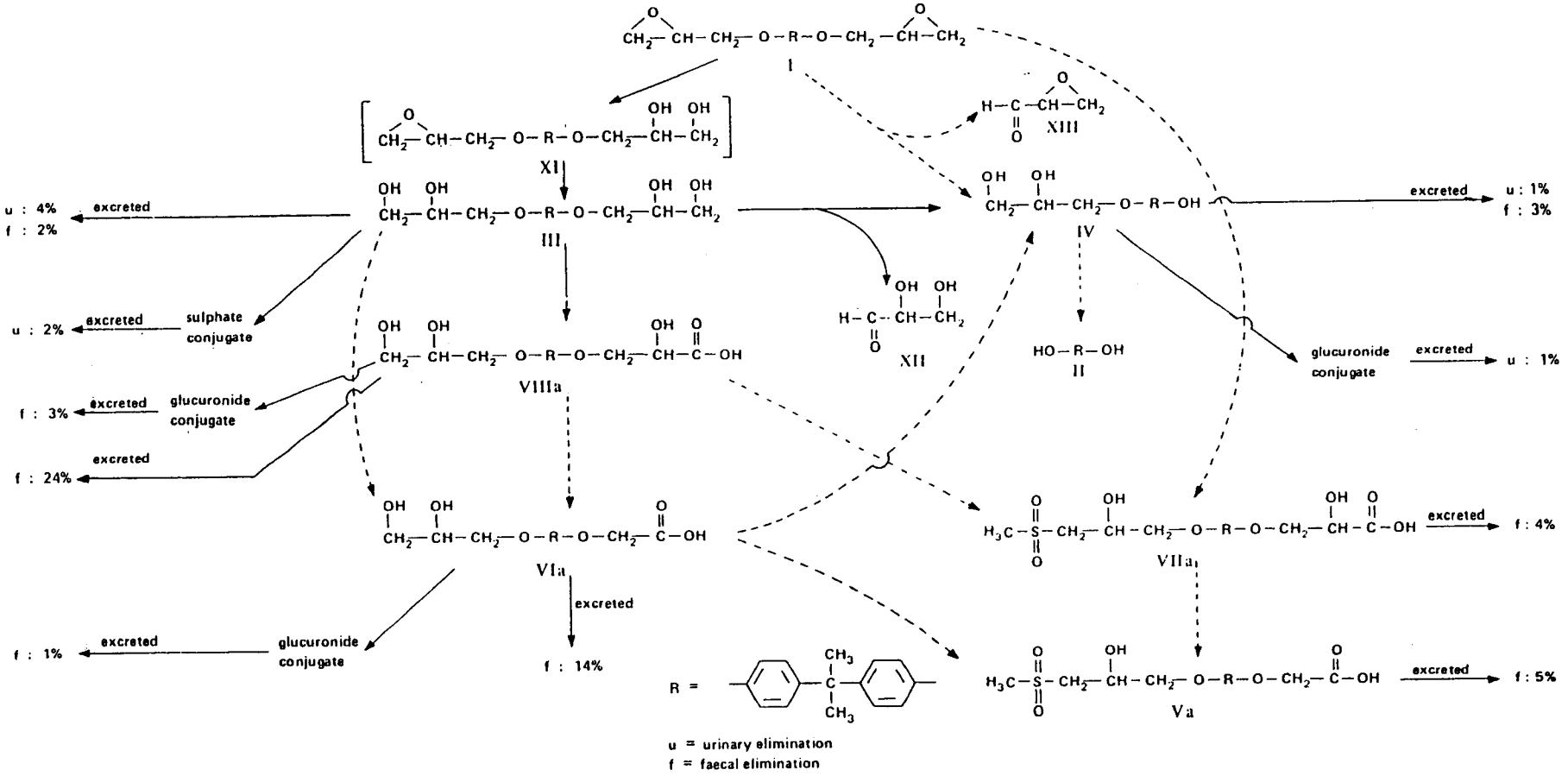


Figure 2 Summary of known and possible metabolic roues to the urinary and faecal metabolites of DGEBPA orally dosed to mice [XI] was isolated in vitro but not in vivo. —known routes; ----- possible routes; I DGEBPA, III bis-diol-DGEBPA; VI phenol-diol-DGEBPA; XII glyceraldehyde; XIII glycidaldehyde (Cli81b).

diol-DGEBPA excreted in the three day period after dosing was on average 10% (2% free) and 2% (0.4% free) of the administered dose for rabbits given 5 mg/kg and 50 mg/kg DGEBPA, respectively (Ead83).

Climie *et al* (Cli81b) could find no indication that glycidaldehyde was produced in an *in vitro* system. Bentley *et al* (Ben89) demonstrated formation of a glycidaldehyde DNA adduct after dermal application of 0.8 and 2 mg DGEBPA per C3H mouse. Steiner *et al* (Ste92) showed that this was a glycidaldehyde-deoxyguanosine adduct. Forming of an adduct indicates that DGEBPA may be directly dealkylated by the skin *in vivo*. At a lower dose (0.4 mg/mouse) no adduct was seen. These results can be explained by the presence of two competing reactions. At lower doses the epoxide hydratase can effectively inactivate DGEBPA before dealkylation occurs and no glycidaldehyde is formed, or in such small amounts that they are inactivated before they interact with the DNA. As the concentration of DGEBPA in the skin increases the inactivation via hydration becomes saturated and some epoxide is dealkylated before hydration occurs. Glycidaldehyde is then produced in increasing amounts and may interact with DNA to produce the adduct. More information about adduct-forming between DNA and glycidaldehyde is given in section 7.1.5.

Conclusion

No information on biotransformation is available after inhalation exposure. In mice the urinary and faecal metabolite profiles of DGEBPA after dermal and oral administration are essentially the same. The main urinary metabolite is bis-diol-DGEBPA, followed by the sulphate conjugate of bis-diol-DGEBPA. The main faecal metabolite is the bis-diol compound oxidized at one side to a carboxylic acid.

6.4 Elimination

See previous paragraphs.

6.5 Biological monitoring

The free and conjugated forms of bis-diol-DGEBPA are determined by HPLC with UV-detection after solvent extraction from hydrolysed urine and extraction column clean-up. The limit of detection ranges from 0.02 to 0.1 µg/ml, with an overall recovery of the metabolite through the analytical procedure of 71%. Data on relationship between exposure and excretion in human beings are not available (Ead83).

A group of 13 workers producing glass fibre reinforced resin pipes collected 24-hour urine samples over the five-day work week and a single spot sample voided after the commencement of the first shift after the weekend. The amount of bis-diol excreted was very low (< 0.01 - 0.17 mg) and in the majority of samples below the analytical limit of detection, which was not given. No cumulative excretion of the bis-diol over the working week could be found. The conclusion was that absorption of DGEBPA was very low, but there were no data on the concentration of DGEBPA in the air (study from 1984, reported by Web93).

6.6 Summary

There is no information on the kinetics of both compounds after inhalation exposure.

Absorption of BPA after oral dosing to rats is rapid. Within three days ± 80% is excreted. The same holds for DGEBPA after oral dosing to mice.

Excretion of DGEBPA after occlusive dermal application to mice depends on the dose and the time period. After 2 days of exposure to 0.4 mg/mouse faecal excretion amounted to 35 - 36% of the dose, whereas a quantity of 2 mg/mouse was excreted for ±10%. Three days after exposure to 1.6 mg/mouse the total faecal excretion amounted to ±20%. Urinary excretion is much less.

In mice the distribution of DGEBPA after dermal and oral administration is essentially the same. Concentrations of less than 1% are found in all organs, in blood and in the remaining carcass. After oral dosing the compound is mainly found in the faeces. Eight days after dermal application a quantity of 9 - 15% remained on the whole skin and 26 - 36% was found on the foil covering.

In mice the urinary and faecal metabolite profiles of DGEBPA after dermal and oral administration are essentially the same. The main urinary metabolite is bis-diol-DGEBPA, followed by the sulphate conjugate of bis-diol-DGEBPA. The main faecal metabolite is the bis-diol compound oxidized at one side to a carboxylic acid.

No biological monitoring method can be indicated for BPA. Biological monitoring of DGEBPA is preferably performed on the urinary metabolite bis-diol-DGEBPA and its sulphate conjugate. The limit of detection ranges from 0.02 to 0.1 µg/ml.

Chapter 7

Effects

7.1 Animal experiments

7.1.1 Irritation and sensitization

Irritation

BPA is a slight skin irritant. Mild irritation effects were caused by 250 mg BPA openly applied to the skin of rabbits. Possible severe eye irritations were caused by exposure to 20 mg BPA for 24 h in rabbits, but the original data cannot be evaluated (Lew92).

After 24-h occlusive exposure to 5% (w/v) BPA in acetone, no irritation was seen on the skin of guinea pigs (Tho77).

Several unpublished studies on skin irritation are reviewed (Web90). Five studies used rabbits, two use guinea pigs. It is concluded that BPA is slightly irritating to rabbit skin following prolonged and repeated application. Slight to moderate irritation has been observed in guinea pigs.

Three unpublished studies deal with eye irritation (Web90). Two studies use rabbits, in the third study the species in unspecified. It is concluded that BPA may be severely irritating to the rabbit eye at concentrations in excess of 1% in certain solvents. The dry powder was slightly irritant while a 10% aqueous suspension was essentially non-irritating.

No topical irritancy was produced by 80% [probably 80% (w/v) in acetone] DGE-BPA (Tho78).

On the other hand, it is reported that DGEBPA is a skin irritant. The skin of rabbits was mildly irritated by 500 mg openly applied DGEBPA.

The only study which reports severe eye irritation is cited by Lewis (Lew92): exposure to 2 mg DGEBPA for 24 h in rabbits caused severe eye irritation. However, the original study is not available, and therefore, cannot be evaluated. On the other hand it is reported (Web93) that DGEBPA and all the Epikote grades tested, irrespective of molecular weight, whether undiluted or formulated in solvent, are non- or at most slightly irritant to the eyes. Also Gardiner *et al* (Gar92) report that DGEBPA-based resins cause only minimal eye irritation.

The incidence of cutaneous irritation caused by DGEBPA (10% (w/v) in acetone, twice weekly) at the site of application during a two-year carcinogenicity study with CF1 mice was assessed macroscopically. In the control group exposure to acetone induced irritant lesions in 16% of males and 14% of females. A higher incidence of irritant lesions, characterized mainly by epilation and skin flaking/scabbing, but inducing ulceration in a few animals, was recorded in the mice of the exposure groups. Forty-two percent, 32%, and 42% of the males and 21%, 21%, and 27% of the females showed signs of skin irritation after exposure to EPON 828, Epikote 828, and pure DGEBPA, respectively. Each group consisted of 50 animals of both sexes (Per88).

After 20 exposure periods of one hour or of seven hours no erythema or oedema was reported. Since this was tested in a Draize test the species was probably the rabbit. Two types of Epikote 828 scored in the Draize test as follows (EEC/OECD score): for erythema after 24 and 72 hr: 1.1 and 1.3; for oedema after 24 and 72 hr: 0.5 and 0.95; for erythema after seven days: 0.9 and 0.6; for oedema after seven days: 0.4 and 0.5, respectively. The primary irritation indexes were 1.8 and 2.15, respectively. A 20% solution of EPON 828 in toluene was slightly more irritating whereas a 20% solution of EPON 828 in acetone was almost non-irritating (studies from 1978, reported by Web93).

Sensitization

When BPA was applied as a solution in a mixture of acetone, dioxane and guinea pig fat on guinea pig skin no reactions were observed in any of the test animals (unpublished results, reported by Web90).

Thorgeirsson and Fregert (Tho77) investigated the sensitizing capacity of DGEBPA-based epoxy resins, using the guinea pig maximization test of Magnusson and Kligman. Twenty albino female guinea pigs of the Hartley strain were exposed to epoxy resins, whereas 15 animals were exposed to BPA or epichlorohydrin. Twenty or 15

animals, respectively, served as controls. The induction was performed with: 0.1 ml Freund's adjuvant, 0.1 ml of the test substance (5.0% (w/v) DGEBPA in acetone, 5% (w/v) epoxy resin (average MW 350) in acetone, 5% (w/v) BPA in acetone, or 5 % (w/v) epichlorohydrin in ethanol), and 0.1 ml of a mixture containing the substance in the vehicle and an equal amount of complete Freund's adjuvant. Challenge was performed two weeks after the second stage of the induction as a 24-hour occluded patch test. The concentrations were a fifth of those used for induction. Simultaneously, a cross-sensitization test was performed by applying the other test substances on the animals as patch tests. All the 20 animals exposed to DGEBPA and to epoxy resin with an average MW of 350 became sensitized. BPA gave no reaction in the 15 animals exposed, and epichlorohydrin sensitized nine of 15 animals. The control animals showed no reactions. No cross-reactions were observed between BPA, DGEBPA-based epoxy resins, and epichlorohydrin (Tho77).

In the same study (Tho77), guinea pig maximization tests were conducted with epoxy resins with a higher average MW. Of 20 animals, 17 reacted to the resin having an average MW of 480, 11 to that of 900, and six to the epoxy resin with an average MW of 1280. Gel permeation chromatography showed that epoxy resins with an average MW of 900 and 1280 contain 10% DGEBPA, and epoxy resin with an average MW of 1850 contains 5% DGEBPA, which is probably the cause of positive reactions in this test (Tho78).

In a further study (Tho78) to investigate the sensitization capacity of epoxy resin oligomers in the guinea pig, three sensitization techniques were used: the guinea pig maximization test, topical exposure with and without sodium lauryl sulphate, and single intradermal injection.

The guinea pig maximization test was performed as described before. Sixty-one animals were sensitized with 5% (w/v) DGEBPA in acetone. One additional series of ten animals were sensitized with 0.5% (w/v) DGEBPA. DGEBPA-based epoxy resins of a higher MW were tested in equimolar concentrations: 28 animals were sensitized with 9.2% (w/v) MW 624 oligomer, 30 animals with 13.5% (w/v) MW 908 oligomer, and 15 animals were sensitized with 17.5% (w/v) MW 1,192 oligomer. DGEBPA produced positive reactions in 56 of 61 animals (92%) sensitized to 5% (w/v) DGEBPA, and in ten of 15 animals (67%) sensitized to 0.5% DGEBPA. The oligomer of MW 624 elicited a reaction in 57% (16/28) of the animals, while after induction and challenge with MW 908 and 1,192 oligomer, the animals showed no positive patch test. In all animals which received the induction and challenge with DGEBPA, no cross-reactions to oligomers with a higher MW were observed. Of the animals treated with the MW 624 oligomer, 29% showed cross-reactions to DGEBPA, but not to the other oligomers. Animals induced and challenged with oligomers with a higher MW showed no cross-reactions to DGEBPA.

Induction and challenge by topical exposure was performed in ten animals. A two by four cm Whatman 3 MM paper was saturated with approximately 0.2 ml of a 20% (w/v) solution of DGEBPA, and applied as a 24-hour closed patch test on a clipped and shaved flank. This procedure was repeated after three days. After two weeks, a patch test was performed on the opposite flank. In another series of 17 animals the clipped and shaved flank was rubbed with 10% sodium lauryl sulphate in vaseline, and a Whatman 3 MM paper was left under occlusion for 48 hours. After two weeks the animals were challenged. Topical sensitization without sodium lauryl sulphate produced no reactions, and with sodium lauryl sulphate 18% (3/17) reacted positive. When the same sensitization procedure was repeated in the same animals 47% (8/17) reacted. These results are inconsistent with those of other investigators; it is unclear whether differences in test material may account for these different observations (Gar92).

Fifteen animals received induction with 0.1 ml of a 20% (w/v) mixture of DGEBPA dissolved in acetone and an equal amount of complete Freund's adjuvant, injected intradermally in the shoulder region. After two weeks, when the animals were challenged as in the maximization test, 30% (3/10) of the animals responded (Tho78).

Several other studies performed with DGEBPA, EPON 828 and Epikote 828, also reveal the skin sensitizing properties of the compound (seven studies performed in 1963-1986, reported by Web93).

Photosensitization

Age-matched female mice were photosensitized to BPA by the application to a clipped site on the rear flank, followed by radiation of the site with UV-B and UV-A. The immunological adjuvantia used were cyclophosphamide, or heat-killed *Corynebacterium parvum (Propionbacterium acnes)*. Five or more days after their first exposure the mice were photochallenged by applying 0.01 ml BPA-solution to the left ear, followed by UV-A to both ears. After this the right ear was challenged with 0.01 ml BPA-solution without further UV-A. Measurements of ear thickness of both ears were taken at 24 h and 48 h post-challenge.

In a typical experiment a group of six female ICR mice were photosensitized to 1% BPA; *C. parvum* was used as adjuvant. Lack of ear swelling in the toxicity group demonstrates the absence of phototoxicity of BPA under the conditions of the photochallenge. The lack of reactivity of the chemical applied to the right ear after UV-A in the group of photosensitized mice, demonstrates the absence of classical allergic contact dermatitis. The left ears were excised from several mice of each group after the 24 hour measurement. In the control group histopathology showed no inflammation. In

contrast, mice of the experimental group showed oedema, and a mononuclear cellular infiltrate.

In a rechallenge experiment UV-A radiation of previously positive challenge sites caused these old photoallergy test sites to flare, evidenced by increased ear thickness. Ears previously challenged by UV-A followed by BPA did not become thickened following UV-A alone challenge.

In four experiments, the author failed to induce any photosensitization of the guinea pig to BPA, although the maximization methods used were successful with other photosensitizers (Mag88).

Cyclophosphamide pretreated female BALB/c mice were induced to BPA by topical treatment of the dorsal skin surface on three consecutive days, and challenged on the ears five days after the last induction. For each induction and challenge treatment mice were irradiated with UV-A and UV-B radiation, 30 min. to one hour after test material application. A 20% solution (w/v) BPA was applied during induction, and 10% (w/v) during the challenge. There were contact allergy, vehicle/radiation, and phototoxicity control groups. Swelling of the ears was measured 24 h after the challenge. A statistically significant difference (p0.001) in ear swelling was found, when photoallergic reactions were compared to control allergy, vehicle/radiation, and phototoxicity control groups (Ger90).

The photoallergic capacity of BPA might be explained by the release of free radicals, during the UV-B-range photodecomposition of BPA (Pel86). Maguire (Mag88) suggested that these radicals may react covalently with nearby macromolecules to form the antigen that is responsible for photoallergy to BPA.

Conclusion

BPA is a slight skin irritant. DGEBPA is a skin irritant. It is not or is at most a slight eye irritant. BPA is not a skin sensitizer in guinea pigs. DGEBPA is a strong skin sensitizer. BPA is a photosensitizer in mice, but not in guinea pigs.

7.1.2 Acute toxicity

A summary of acute toxicity data of BPA is given in Table 6 and of DGEBPA in Table 7. The acute toxicity is low for both compounds via the oral and dermal routes of exposure. Signs of intoxication of oral BPA administration include initial excitability, followed by depression, ataxia, occasional spasms and hind limb paresis. Others report atonia, severe diarrhea and diuresis (Web90).

Signs of intoxication after ip injection of BPA include vasiculation, tremors, prostration, loss of consciousness and roughening of the coat (Web90).

Signs of intoxication of DGEBPA include depression, weight loss and slight difficulty in breathing (Web93). After dermal application of DGEBPA skin irritation has been observed (Web93).

Conclusion

According to the EC classification (EC93) BPA and DGEBPA are of a low order of acute toxicity upon oral and dermal administration. Due to the low vapour pressure of BPA and DGEBPA, and the lack of data, their inhalation toxicity cannot be assessed.

7.1.3 *Short-term toxicity*

BPA, sc implant, mice

Groups of eight CD-1 mice of each sex were continuously exposed to BPA via subcutaneous Silastic implants, containing 0, 6.25, 12.5, 25, 50, or 100 mg BPA suspended in corn oil for a period of two weeks. No treatment-related deaths or changes in body weight gain were observed, but a no statistically significant increase in female reproductive tract weight was seen. Therefore, dose levels of 0, 25, 50, and 100 mg BPA were selected for reproduction and fertility assessment by continuous breeding (section 7.1.6) (Ree84).

BPA, oral administration, mice

Eight male and eight female CD-1 mice per dose group were given 0, 0.31, 0.62, 1.25, 2.5, or 5% BPA in their feed for 14 days, equivalent to approximately 310, 620, 1250, 2500 or 5000 mg/kg body weight. No clinical signs of toxicity were observed in either male or female mice in the 0, 0.31, 0.62, and 1.25% BPA dose groups. In the 2.5% BPA-treated group, both male and female mice exhibited clinical signs of toxicity, including dehydration, dyspnoea, lethargy, tremors, and ptosis. In the 5.0% BPA dose group dehydration, dyspnoea, lethargy, piloerection, diarrhea, ptosis, and moribundity were observed in both male and female mice. During the 14-day exposure six males and six females in the 5.0% BPA group died, but no deaths occurred in the other dose groups. For those animals that survived, the percent combined weight gain was significantly depressed ($p < 0.01$) in the 1.25, 2.5, and 5.0% BPA groups relative to the controls. Based on these results, dietary levels of 0, 0.25, 0.5, and 1.0% BPA were selected for reproduction and fertility assessment by continuous breeding (section 7.1.6) (Ree85).

Table 6 Acute toxicity data of BPA.

species	route of entry	dose or concentration	acute effect	reference
rat	oral	3250 mg/kg (agar)	LD_{50}	Lew92
rat	oral	5660 mg/kg (DMSO)	LD_{50}	Web90
rat	oral	4240 mg/kg	LD_{50}	Mor87
rat	oral	> 12,000 mg/kg	LD_{50}	Web90
rat	oral	6500 mg/kg	LD_{50}	Web90
rat	oral	± 3200 mg/kg	LD_{50}	Web90
Sherman rat	oral	4040 mg/kg	LD_{50}	Web90
Fischer 344 rat, male	oral	4100 mg/kg	LD_{50}	NTP82
Fischer 344 rat, female	oral	3300 mg/kg	LD_{50}	NTP82
rat	inhalatory	1898 mg/m^3 [a]	LC_{50}	Lew92
rat	inhalatory	> 170 mg/m^3	LC_{50}	Web90
rat	intraperitoneal	400 - 800 mg/kg	LD_{50}	Web90
mouse	oral	± 1600 mg/kg	LD_{50}	Web90
mouse	oral	2400 mg/kg	LD_{50}	Web90
mouse	oral	2500 mg/kg	LD_{50}	Lew92
$B6C3F_1$ mouse, male	oral	5200 mg/kg	LD_{50}	NTP82
$B6C3F_1$ mouse, female	oral	4100 mg/kg	LD_{50}	NTP82
mouse	intraperitoneal	150 mg/kg	LD_{50}	Lew92
mouse	intraperitoneal	± 200 mg/kg	LD_{50}	Web90
rabbit	oral	2230 mg/kg	LD_{50}	Lew92
rabbit	oral	4000 mg/kg	LD_{50}	Web90
rabbit	dermal	3000 mg/kg	LD_{50}	Lew92
rabbit	dermal	3600 mg/kg	LD_{50}	BIB89
rabbit	dermal	6400 mg/kg (40% in DMSO)	1/5 died	Web90
		2000 mg/kg (10% in propylene glycol)	3/15 died	
guinea pig	oral	4000 mg/kg	LD_{50}	Web90
mammal	oral	6500 mg/kg	LD_{50}	RTE92

[a] Number of hours of exposure not reported.

In a preliminary study to establish a MTD for the chronic study, ten male and female $B6C3F_1$ mice were fed with 0, 5000, 10,000, 15,000, 20,000, or 25,000 ppm BPA in the diet, corresponding to approximately 500, 1000, 1500, 2000, and 2500 mg/kg/day, for a period of 13 weeks. Two of ten female mice receiving 5000 ppm died, but no other deaths occurred. Weight gain was depressed by 14% or more in male mice receiving 15,000 to 25,000 ppm, and by 17% or more in all dose groups of female mice. The depression in weight gain was not dose related in females. Multinucleated giant hepatocytes were observed in all dosed groups of male mice with an incidence and severity that were dose related. Multinucleated giant hepatocytes were found in 9/10 males receiving the highest dose, compared with 0/10 female mice receiving this dose. Doses selected for the chronic study were 1000 and 5000 ppm BPA in feed for male mice, and 5000 and 10,000 ppm for females (NTP82).

Table 7 Acute toxicity data of DGEBPA.

species	route of entry	dose or concentration	acute effect	reference
rat	oral	11,000 mg/kg	LD_{50}	Lew92
rat	oral	21,600 mg/kg	LD_{50}	Web93
rat	intragastric	11,400 mg/kg	LD_{50}	Hin81
rat	intraperitoneal	2,400 mg/kg	LD_{50}	Hin81
rat	dermal	>1,600 mg/kg	LD_{50}	Web93
rat	dermal	>1,600 mg/kg	LD_{50}	Gar92
rat	subcutaneous	2,580 mg/kg	LD_{50}	Hin58
rat	inhalatory	>saturated, 8 hours	no deaths observed	Hin81
mouse	intragastric	15,600 mg/kg	LD_{50}	Hin81
mouse	intraperitoneal	4,000 mg/kg	LD_{50}	Hin81
mouse	dermal	>1,200 mg/kg	LD_{50}	Web93
mouse	dermal	>800 mg/kg	LD_{50}	Gar92
rabbit	intragastric	19,800 mg/kg	LD_{50}	Hin81
rabbit	dermal	>22,000 mg/kg	LD_{50}	Web93
rabbit	dermal	20,000 mg/kg	LD_{50}	Hin81

BPA, oral administration, rats

BPA was fed to groups of five male and five female rats for two weeks in a concentration of 0, 2000, 4000, 8000 and 12,000 ppm in the diet. There were no clinical signs of intoxication. Dose-related decreases in body weight were seen in males at the three highest dose levels and in females at 8000 and 12,000 ppm. Food consumption was slightly decreased for male rats at 8000 and 12,000 ppm. There were no compound-related gross pathologic lesions. The two-week dietary no-effect levels were: 2000 ppm for male rats and 4000 ppm for female rats (study from 1976, reported by Web90).

Groups of ten male and ten female Wistar rats were fed 0, 400, 2000 and 10,000 ppm BPA in the diet for four weeks. The general condition, behavior, and survival were not adversely affected at any dose level. Growth, food intake and food efficiency were markedly decreased at 10,000 ppm in both sexes. Gross autopsy did not reveal any treatment-related changes. The four week dietary no-effect level was 400 ppm for rats (study from 1979, reported by Web90).

In an 8-week study 30 - 40 male and female rats were fed 10,000 ppm BPA in the diet. Body weight gain was significantly reduced in both sexes but there were no other ill effects (study from 1959, reported by Web90).

Three studies were performed feeding rats during 90 days with BPA. One study added 8000 ppm BPA to the diet and found no deleterious effects (study from 1967, reported by Web90). The second study added 0, 100, 500 and 2500 ppm BPA to the diet. Groups of 15 male and 15 female Wistar rats were used. There were no deaths in any treatment or control group. Clinical signs were confined to slight alopecia at the top

dose level in both sexes. Gross pathological examination revealed enlarged caeca in both sexes at 2500 ppm and in the 500 ppm group males. Microscopic examination did not reveal any abnormalities, full examination was confined to top dose animals. The 90-day dietary no-effect level was 500 ppm for rats (study from 1979, reported by Webb 1990). The third study used a range of 2 - 520 mg/kg/day, added to the diet of groups of five male and five female Sherman rats. No overt signs of toxicity and no microscopic changes which could be attributed to the compound at any dose level. The upper intestine, kidney, liver and spleen were examined. It is concluded that the 90-day no-effect level for rats is 520 mg/kg/day (study from 1951, reported by Web90).

In a preliminary study to establish a maximum tolerated dose (MTD) for the chronic study, ten male and female F344 rats were fed with 0, 250, 500, 1000, 2000, or 4000 ppm BPA in the diet, corresponding to approximately 12.5, 25, 50, 100, and 200 mg/kg/day, for a period of 13 weeks. Two of ten male rats receiving 1000 ppm died, but no other deaths were seen. Weight gain was depressed 18% or more in males receiving at least 1000 ppm, and by more than 10% in females receiving 1000 ppm or more. Feed consumption was not affected. Hyaline masses were found in the bladder lumen of 4/10 male rats receiving 4,000 ppm, 6/10 receiving 2000 ppm, 3/10 receiving 500 ppm, and 5/10 receiving 250 ppm, compared with none in control male rats. Caecal enlargement was noted in 60-100% of the animals of each dose group, with the exception of females treated with 250 ppm BPA, and was considered to be compound related. No inflammatory changes of other mucosal abnormalities were detected when the cell walls were examined histologically. Based on the data for weight gain depression, doses selected for the chronic study were 1000 and 2000 ppm BPA in feed (NTP82).

BPA, oral administration, other animals

A group of 13 rabbits were given 500 mg BPA/kg via the oral route during two months. No significant effect on body weight or condition was observed. The erythrocyte count was reduced as were blood phospholipids. At the end of the experiment spleen/body weight ratios were increased while adrenal/body weights ratios were decreased (report from 1968, reported by Web90).

A 2-week range finding study with one male and one female Beagle dog per dose group used 2000, 4000, 8000, and 12,000 ppm BPA in the diet. Pretreatment measurements served as controls. There were no clinical signs of intoxication, nor treatment-related changes in body weight or food consumption. There were no gross lesions, however there were several cases of focal mucosal congestion and haemorrhage of the gastrointestinal tract (study from 1976, reported by Web90). In the subsequent study four male and four female Beagle dogs were fed with a diet containing 0, 1000, 3000,

or 9000 ppm BPA for 90 days. There were no compound-related changes in general behavior and appearance, body weight, food consumption, ophthalmoscopy, haematology, biochemistry or urinalysis. Pathological examination revealed no gross lesions. At 9000 ppm mean liver weights were significantly higher than the control group. It is concluded that the 90-day no-effect level for dogs is 3000 ppm. The only effect at 9000 ppm was an increase in liver weight (study from 1976, reported by Web90).

BPA, inhalation exposure, rats

In an inhalation study with four male Alderley Park rats five exposures of six h to a saturated atmosphere induced no signs of intoxication. There are no data on how this atmosphere was obtained. Upon autopsy the organs were normal (study from 1970, reported by Web90).

Groups of 20 male and 20 female Fischer rats were exposed to 0, 10, 50, or 150 mg BPA/m^3 (almost maximum attainable concentration), 6 hr/day, 5 d/week for nine exposures. The particle size ranged from 2.6 to 6.2 micron. Necropsies were performed the day after the last exposure and 29 days later. Full histopathological examination of tissues was confined to top dose and control animals. At 10 and 50 mg/m^3 only the respiratory tract was examined and this was also the case with all the recovery groups. It is concluded that the nine exposure no-effect level for rats is 10 mg/m^3. At higher dose levels inflammation of the anterior part of the nasal cavity and hyperplasia of the nasal epithelium have been observed (study from 1985, reported by Web90).

A subchronic study comprises the exposure of 30 male and 30 female Fischer rats per group to 0, 10, 50 and 150 mg BPA/m^3, 6 hr/day, 5 d/week for 13 weeks. The highest concentration is the almost maximum attainable concentration. Mass median aerodynamic diameter of the particles (depending on the method) range from 1.5 to 5.2 micron. Ten males and ten females were necropsied 1, 28 and 84 days after the last exposure. Porphyrin-like reddish staining around nose and perineal soiling in both sexes were observed at 50 and 150 mg/m^3 and in some females at 10 mg/m^3. Reddish nasal staining occurred in some males at 10 mg/m^3. These effects were not progressive as exposure continued and regressed within seven days of cessation of exposure to 150 mg/m^3. Body weights (mean of up to 30 rats/group) were decreased significantly throughout the study in the 50 and 150 mg/m^3 exposure groups. At 10 mg/m^3 body weights were reduced for most of the exposure period but were comparable to control values at the end of the exposure period. There were no changes in haematological or clinical chemical parameters considered biologically significant. The only treatment-related histopathological changes were observed in the nasal cavity. A dose-related very slight to slight hyperplasia of the stratified squamous epithelium (ventral meatus) and respiratory epithelium (adjacent to vomeronasal organ) and very slight to slight

chronic inflammation of the underlying submucosa was observed at 50 and 150 mg/m^3 in the anterior part of the nasal cavity. There was also slight to moderate hyperplasia of the goblet cells on naso- and maxilloturbinates and the lateral nasal wall. Twelve weeks after cessation of exposure there were no gross or microscopic pathological changes attributable to treatment. It is concluded that the 90-day no-effect level for rats was 10 mg/m^3. Hyperplasia and inflammatory changes observed in the anterior nasal cavity at higher dose levels were fully reversible within 12 weeks of cessation of exposure (study from 1988, reported by Web90).

DGEBPA, oral administration, rats

Rats were fed DGEBPA in their diets for three months at concentrations up to 3%. Rats at the highest dose level rejected the diets and failed to gain weight; these rats showed effects on gross and histopathologic examination that were consistent with malnutrition. There was no evidence of systemic toxicity at any level (study from 1958, reported by Gar92).

In another subchronic study, DGEBPA was fed to rats at dietary concentrations of 0.2, 1, and 5% for 26 weeks. All rats at the highest dose died by the end of 20 weeks, but gross and histopathologic examination did not reveal evidence of systemic toxicity at any dose (study from 1958, reported by Gar92).

Administration of a low molecular weight DGEBPA-based resin (Araldite GY250) by gavage to rats for 28 days at doses of 0, 50, 200 and 1000 mg/kg/day did not alter a large range of parameters, a.o. gross pathology, histopathology, clinical observations, haematology and blood chemistry (study from 1984, reported by Gar92).

DGEBPA, ip injection, mice

To investigate lung tumours, 30 male mice of the Heston A strain received intraperitoneal injections of 4.0 g/kg epoxy resin B1, a commercial DGEBPA resin, [type and quantity of impurities unspecified], 95% in acetone every other day for 16 weeks. There was an acetone control group of 30 males in which six mice developed a pulmonary adenoma. The incidence in mice injected with epoxy resin B1 was between zero and seven tumours [not exactly specified]. There was no statistical difference between the incidence in treated mice and controls (Hin58). Due to imperfections in data presentation no conclusions can be drawn.

Conclusion

BPA

Subcutaneous implantation of BPA had no effects on mice in dosages up to 100 mg.

Oral dosing via the diet of 5% BPA for two weeks killed six out of eight mice. At 2.5% BPA mice showed dehydration, dyspnoea, lethargy, tremors, and ptosis. Feeding of 15,000 to 25,000 ppm for 13 weeks depressed weight gain in male mice. In female mice weight gain was depressed after feeding BPA from 5000 ppm upward, but not dose-related. Multinucleated giant hepatocytes were observed in male mice after feeding BPA from 5000 ppm with a dose-related increase and severity.

In rats 8000 - 12,000 ppm BPA in the diet reduced body weight gain after two, four and eight weeks. Feeding rats 2500 ppm BPA for 90 days induced slight alopecia. Enlarged caeca were observed after feeding from 500 ppm upward in female rats and from 250 ppm upward in males. No microscopic abnormalities were found. Hyaline masses were found in the bladder of male rats, there was no dose-related increase.

Feeding dogs for 90 days with 9000 ppm BPA increased the mean liver weight. No other changes were observed. No effects were observed after feeding 3000 ppm.

The almost maximum attainable concentration in air, 150 mg/m^3, and 50 mg/m^3, induced porphyrin-like reddish staining around nose and perineal soiling in rats, decreased body weight, and very slight to slight hyperplasia and chronic inflammation in the nasal cavity. The effects are reversible upon cessation of exposure. The 90-day no-effect level for rats was 10 mg/m^3.

DGEBPA

The feeding of DGEBPA to rats at dietary concentrations up to 30,000 ppm for three months does not induce systemic toxicity. However, dosages of 50,000 ppm induced death in 100% of the rats by the end of 20 weeks, mainly due to malnutrition.

7.1.4 *Long-term toxicity/carcinogenicity*

BPA, oral administration, mice and rats

The following describes a NTP study from 1982.

BPA (containing five unidentified minor impurities, one occurring at 1.8%) was administered to 50 F344 rats of either sex (1000 or 2000 ppm in the diet), to 50 male B6C3F$_1$ (1000 or 5000 ppm in the diet), and to 50 female B6C3F$_1$ mice (5000 or 10,000 ppm in the diet) for a period of 103 weeks. The administered doses corresponded to approximately 74 and 148 mg/kg/day in male rats, 74 and 135 mg/kg/day in female rats, 100 and 500 mg/kg/day in male mice, and 500 and 1000 mg/kg/day in fe-

male mice. Groups of 50 rats and 50 mice of either sex served as controls. The survival among all groups of animals was comparable in both species and sexes. Two control male mice and two high-dose female mice were accidently killed and were censored from statistical analysis. Mean body weights of treated rats of either sex, of low- and high-dose female mice, and high-dose male mice were lower than those of the controls. Food consumption of dosed male rats was 90% that of controls. Food consumption of dosed female rats was only 70 to 80% that of the controls throughout most of this study and was probably the cause of reduced body weight gain. Food consumption among all groups of mice appeared to be similar.

Leukaemias of the haematopoietic system occurred in male rats at increased incidences in the high-dose group (13/50 controls, 12/50 low-dose, 23/50 high-dose). This was a significant trend in the positive direction ($p = 0.021$). The high-dose group had a significantly higher incidence ($p = 0.030$), when compared to the controls, but this is above the value of $p = 0.025$ required by the Bonferroni inequality criterion for an overall significance of $p = 0.05$, when two dosed groups are compared with a control group. Neither trend, nor higher incidence were significant after life table analyses, which adjust for intercurrent mortality. The increased incidences in dosed female rats were not statistically significant (7/50, 13/50, 12/50). Lymphomas or leukemias of the haematopoietic system in male mice were observed in increased proportion in the low-dose group compared with the other two groups (2/49, 9/50, 5/50). The difference between low-dose and control group was significant ($p = 0.028$), but this is above the value of $p = 0.025$ required by the Bonferroni inequality criterion for an overall significance of $p = 0.05$, when two dosed groups are compared with a common control group. No significant incidence was observed in high-dose males as well as in female mice (incidence: 13/50, 10/48 and 8/48).

Interstitial-cell tumours of the testis occurred at statistically significant incidences in low-dose (48/50; $p = 0.001$), and high-dose (46/49; $p = 0.003$) rats when compared with controls (35/49). However, since this lesion normally occurs at high incidence in aging F344 male rats, the increased incidence observed in this study was not considered compound related.

A compound related increase of multinucleated giant hepatocytes was observed in male mice (1/49, 41/49, 41/50), but there was no increase of liver tumours. Extensive histopathological examination did not reveal any other effect on liver and kidney of both species and sexes.

Due to a high background incidence and high variation between the treatment groups there is no convincing evidence that BPA is carcinogenic for F344 rats or $B6C3F_1$ mice of both sexes under the conditions of this bioassay. The lowest dose tested, 74 mg/kg/day reduced the body weight gain in male and female rats. Female rats were more sensitive to this effect. Extensive histopathological evaluation of the

liver and the kidney revealed only multinucleated giant hepatocytes in both dose groups of male mice (100 and 500 mg/kg/day) (NTP82).

DGEBPA, dermal application, mice and rabbits

Thirty male C3H mice received skin application of 0.3 % epoxy resin B1, a commercial DGEBPA resin, dissolved in acetone once a week or 5% once or three times weekly for 24 months [type and quantity of impurities unspecified]. The control mice received 0.2 ml acetone three times weekly. From a total of 240 mice 104 animals survived. It is not specified in which treatment group this occurred and what was the cause of death. No tumours were seen in the control and treated groups (Hin58). Due to a high death rate and the unknown purity of the compound no conclusions can be drawn.

In another skin painting study in mice, "one brushful" of undiluted resin was applied to the skin of C3H mice three times weekly for up to 23 months. A skin papilloma was detected in a single mouse after 16 months of treatment, at which time 32 of the 40 mice started on the study were still alive (Wei63). When the study was repeated, twice for 24 months and once for 27 months, no skin tumours were found (Wei63).

In a study conducted on C3Hf/Bd mice with specified technical-grade DGEBPA obtained from three different manufacturers, no treatment related skin neoplasms were found after skin application of 75 mg/week for two years (cited by Zak85; the original article was not available in The Netherlands).

A study from 1987 is reported (Gar92): The carcinogenic potential and chronic dermal toxicity of three commercially available DGEBPA-based resins were investigated. The test materials were dissolved in acetone, and 50 µl was applied topically, twice a week, for 94 weeks, to the backs of C3H/HeJ male mice, 50 animals per treatment group. The three DGEBPA-based resins tested were 42% DGEBPA, 76% DGEBPA, and 27% DGEBPA, and were tested in acetone at concentrations of 50%, 25%, and undiluted, respectively. Thus, the actual concentrations of DGEBPA applied were 21, 19, and 27%. Two groups of 50 mice each were treated twice weekly with 50 l of acetone or 0.025% benzo[a]pyrene in acetone to serve as negative and positive control groups, respectively. An additional group of 50 mice received no treatment as a negative control group. The skin from all animals was examined by light microscopy for nonneoplastic and neoplastic lesions, and histopathologic examination of internal organs was conducted on half of the mice from each group. Forty-eight of the mice in the positive control group developed skin tumours, with an average latent period of 32.4 weeks, whereas no skin neoplasms were observed in either of the negative control groups or in the groups treated with resins in acetone at a final concentration of 19 or 27% DGEBPA. Three of the fifty mice treated with test material containing 21%

DGEBPA in acetone had microscopically detectable skin papillomas, but no malignant neoplasms of the skin were present in any of the animals in this treatment group. The incidence of hepatocellular carcinoma observed in the treated and control groups was within the range of those detected in historical control animals from the same laboratory and below values reported by the animal supplier for this strain of mouse.

Fifty male and 50 female CF1 mice were treated with acetone once a week or twice a week with 1% or 10% (v/v) technical DGEBPA (Araldite GY250, containing 4.3 ppm epichlorohydrin) in 0.2 ml acetone for a period of two years. The 10% concentration was determined to be the maximum tolerated dose. There was no effect on survival and no skin tumour was observed at the site of application. High incidences of malignant lymphomas in the lymphoreticular tissues and of pulmonary adenomas and carcinomas were found in both treated and control groups, but there was no statistical evidence for a treatment related effect (Zak85).

Groups of 50 male and 50 female CF1 mice were treated with pure DGEBPA, EPON 828 (<29 ppm epichlorohydrin) or EPIKOTE 828 (<3 ppm epichlorohydrin) dissolved in acetone (1 or 10% w/v) twice weekly (0.2 ml/dose) over a period of two years. The doses of the epoxy resins were selected on the basis of a preliminary 4-week cutaneous irritancy study. The control group consisted of 100 animals of both sexes and was treated with acetone alone. Survival of the CF1 mice was unaffected by cutaneous exposure to each epoxy resin and the etiology of death or terminal illness was not influenced significantly by treatment. The incidence of cutaneous tumours of the treated site or of the skin at all sites was not statistically significant when compared with acetone controls. There were no metastases of cutaneous or subcutanuous tumours.

The incidence of renal tumours in males treated with EPON 828 gave rise to a significant trend ($p = \pm 0.03$), control: 6/99, 1%: 0/50, 10%: 8/50. However, renal neoplasms are common in CF1 mice bred in the laboratory of the authors, the absence of this tumour in the 1% dose group is rather unusual. In the parallel studies with EPIKOTE 828 and pure DGEBPA none of the treated male groups had renal tumours at an incidence significantly greater than in the control group. There were significant trends ($0.05 > p > 0.01$) for the number of females treated with EPIKOTE 828 with reticulum-cell sarcoma (16/99, 11/50, 15/50) and lymphoblastic sarcoma (4/99, 2/50, 4/50). A significant trend was also seen for the total number of females with at least one systemic tumour and also for the number with a tumour of the lymphoreticular/haematopoietic tissue. The only significant trend ($0.05 > p > 0.01$) for treatment with pure DGEBPA was the incidence of thymic lymphosarcomas in females (7/99, 2/50, 5/50). However, the authors think it is likely that the CF1 mice used are susceptible to the development of tumours of lymphoreticular/haematopoietic tissues as a result of the presence of a virus and/or a genetic tendency to viral infection. It is

possible, therefore, that the increased incidence of reticulum cell-sarcomas or lymphosarcomas in female mice after treatment with EPIKOTE 828 or pure DGEBPA is not a direct or valid indication of any systemic carcinogenic potential of these epoxy resins (Per88).

Hine *et al* (Hin58) treated a group of 16 male albino rabbits with acetone, two epoxy resins and 20-methylcholanthrene on a predesignated shaved area. Each animal received all three compounds simultaneously on different areas of the body, therefore no conclusions can be drawn.

DGEBPA, oral administration, mice

Male mice of the Heston A strain were fed with a diet containing 0.2% of epoxy resin B1 [type and quantity of impurities unspecified]. The daily intake of each mouse was 5-6 mg resin for a period of 11 months. After termination the animals were investigated for lung tumours. In the control group 29/30 survived and 15/29 developed lung tumours, four of which had multiple tumours (two to five per mouse). Of the 30 treated mice 23 survived and 12/23 developed lung tumours, one of which was multiple (two tumours). This difference was not statistically significant (Hin58). Due to a high death rate and the unknown purity of the compound, no conclusion can be drawn.

DGEBPA, subcutaneous injection, rats

Male rats of the Long-Evans strain were given three injections of epoxy resin B1 [type and quantity of impurities unspecified] 50% in propylene glycol once a week for 24 months. The total amount injected was equal to the LD_{50}: 2580 mg/kg body weight. Controls received propylene glycol alone. Among the controls 17/30 survived and no tumours were found at the site of injection. Elsewhere five malignant tumours appeared. No details are provided on place or type of the tumours. In the treated group 14/30 survived; in the surviving rats four fibrosarcomas were found at the site of application with seven malignant tumours appearing elsewhere. These animals died during the experimental period. None of the survivors had neoplasms at the injection site, although all of them had foreign body reactions, not further specified. The sarcomas formed at the injection site are not considered very relevant for human risk evaluation, because rats are unusually susceptible to subcutanuous implantations (Hin58). Although there is a high death rate, both among the control and the treated animals, it can be concluded that DGEBPA probably does not induce systemic tumours in rats after multiple subcutaneous injections.

Conclusion

There was no convincing evidence that BPA was carcinogenic for F344 rats of B6C3F$_1$ mice of either sex after *oral administration.*

After *dermal application and subcutaneous injections* of pure and commercial DGEBPA no skin tumours developed in rats and mice. Although lymphoreticular tumours were increased in some groups of some experiments, the data lacked consistency and therefore the increase of this spontaneously occurring tumour is not considered indicative of a carcinogenic potential of the compound.

7.1.5 *Mutagenicity*

A summary of data on mutagenicity of BPA is given in Table 8 and of DGEBPA in Table 9.

The reaction of DGEBPA with DNA was studied *in vivo* (Ben89 and Ste92).

Bentley *et al* (Ben89) applied 0.4, 0.8 or 2 mg radiolabeled DGEBPA to shaved dorsal skin of C57BL6 and C3H mice. After 48 hours the mice were killed and the skin of four pooled animals was treated to extract and isolate proteins, RNA and DNA. Despite the fact that most of the radioactivity was found to bind to protein and RNA, a DNA adduct was detected, which co-chromatographed with a glycidaldehyde-deoxyguanosine adduct. More radioactivity was associated with DNA isolated from C3H mice than from C57BL6 mice. No formation of an adduct was seen at the lowest dose tested.

Steiner *et al* (Ste92) showed that the adduct formed was not a glycidaldehyde-deoxyguanosine adduct, but that adenine residues are the major target of metabolically formed glycidaldehyde. Nine male C3H mice were treated with a single topical dose of 2 mg DGEBPA in 100 l acetone and were killed after 48, 96, or 192 hours. Two mice were treated with 2 mg glycidaldehyde in 100 l acetone and were killed after 24 hours of exposure. Control mice received acetone alone and were killed after 192 hours. Epidermal DNA was isolated and aliquots of hydrolysed DNA were separated by HPLC and analyzed by fluorescence emission. All epidermal DNA hydrolysates from mice treated with DGEBPA or glycidaldehyde contained hydroxymethylethenodeoxyadenosine-3'- monophosphate (HMEdAp), not hydroxymethylethenodeoxyguanosine-3'-monophosphate (HMEdGp). This adduct was not detectable in DNA samples obtained from animals treated with acetone alone. The amounts of adducts measured in mice treated with DGEBPA for different exposure times were 0.5 adducts/10^6 nucleotides after 48 h, 0.1 adducts/10^6 nucleotides after 96 h and 0.3

adducts/10^6 nucleotides after 192 h respectively. In glycidaldehyde-treated mice 166 adducts/10^6 nucleotides could be detected. The limit of detection using this assay was ~30 fmol in the presence of 1.6 mol natural nucleotides (0.02 adducts/10^6 nucleotides). A comparison of the adduct levels after treatment with DGEBPA and glycidaldehyde allows a calculation of the bioavailability of glycidaldehyde from DGEBPA. The results show that a dose of 2 mg glycidaldehyde leads to the formation of 166 HMEdAp/10^6 nucleotides. Treatment with 2 mg DGEBPA resulted, at the most (one mouse after 48 h of exposure), in formation of 0.8 HMEdAp/10^6 nucleotides. Under the assumption of a linear dose versus adduct-level relationship, this would be equal to a dose of 10 µg glycidaldehyde. Since 2 mg DGEBPA contains 0.85 mg glycidaldehyde equivalents at the most 1.1% of the glycidaldehyde moiety in DGEBPA was available for DNA adduct formation.

The weak activity of DGEBPA to form DNA adducts is supported by the weak *in vivo* mutagenicity of glycidaldehyde (Bar83, Bar89, Vog90).

Conclusion

BPA does not induce mutations in bacteria, does not induce chromosomal aberrations, sister chromatid exchanges, or transformations in mammalian cells *in vitro*.

DGEBPA is mutagenic in some bacterial test systems. It probably causes basepair substitutions rather than frameshift mutations. In higher dosages (0.8 mg/mouse) DGEBPA or a metabolite may react with DNA in mammals *in vivo* after dermal application. DGEBPA may induce neoplastic transformations, gene mutations and chromosomal aberrations in mammalian cells *in vitro*. It is negative in the host-mediated assay. It does not induce UDS in human cells *in vitro*. No induction of micronuclei, dominant lethality or DNA single strand breaks are observed in mammals *in vivo*.

7.1.6 *Reproduction toxicity*

BPA, rats

Young adult female Sprague-Dawley rats (250-300 g) were treated with 85 mg/kg (four animals) or 125 mg/kg (12 animals) BPA dissolved in corn oil and injected daily intraperitoneally from the first day of gestation through the 15th day. The highest dose was the maximum tolerated dose. A control group of 12 rats received ip injections of corn oil. On day 21 of gestation the females were killed and litters and maternal organs were collected. The higher dosage significantly ($p = 0.0014$) impaired the establishment of pregnancy of sperm-positive rats and both doses caused a significant ($p <$

Table 8 Mutagenicity data of BPA.

type of test	species	concentrations tested	remarks	results	references
Ames	*Salmonella typhimurium* TA1538	0.1-1.0 mg/ml in liquid suspension cultures; 0.2-500 µg/plate	with and without RLiA[a]	- -	study from 1978, reported by Web90
Ames	*Salmonella typhimurium* TA100, TA1535	not reported	with and without RLiA	-	And78
Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	-333 µg/plate	with and without RLiA	-	Ten86 and Ten87
Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	0 - 333.3 µg/plate	with and without RLiA and HLiA[b]	-	Haw83
reversed mutation	*Escherichia coli* WP2 and WP2 uvrA	0.1-1.0 mg/ml in liquid suspension cultures; 0.2-500 µg/plate	with and without RLiA	- -	study from 1978, reported by Web90
UDS	primary rat hepatocytes	not reported		-	Ten86
mitotic gene conversion	*Saccharomyces cerevisiae* JDI	0.01-0.5 mg/ml	with and without RLiA	-	study from 1978, reported by Web90
chromosomal aberration	RL4 (rat liver) cells	0-30 µg/ml		-	study from 1978, reported by Web90
chromosomal aberration	chinese hamster ovary cells	-50 µg/ml		-	Ten86 and Ten87
chromosomal aberration	chinese hamster ovary cells	0 - 50 µg/ml	with and without RLiA	-	Ive89
sister chromatid exchange	chinese hamster ovary cells	-50 µg/ml		±	Ten86 and Ten87
sister chromatid exchange	chinese hamster ovary cells	0 - 25 µg/ml	with and without RLiA	-	Ive89
thymidine kinase locus	L5178Y mouse lymphoma cells	-50 µg/ml		-	Ten86 and Ten87
thymidine kinase locus	L5178Y mouse lymphoma cells	0 - 60 µg/ml	with and without RLiA; 60 g/ml is lethal	-	Myh91
transformation assay	Syrian hamster embryo cells	0 - 60 µg/ml		-	Jon88
transformation assay	Balb/c 3T3 cells	not reported	with and without RLiA	-	Ten86
sex-linked recessive lethality	*Drosophila melanogaster*	feeding 10 g/kg for 3 days	surviving males were mated	-	Fou94
dominant lethality	male Sprague-Dawley rats	85 mg/kg/day ip inj. on 5 consecutive days		-	study from 1980, reported by Web90

[a] Rat liver activation.

[b] Hamster liver activation.

Table 9 Mutagenicity data of DGEBPA.

type of test	species	concentrations tested	remarks	results	references
Ames	*Salmonella typhimurium* TA100, TA1535	0 - 54 µmol/plate	with and without RLiA[a]	+	And78
Ames	*Salmonella typhimurium* TA1535, TA98	0.5 - 2.0 µmol/plate	with and without RLiA with and without RLiA	± -	study from 1977, reported by Gar92
Ames	*Salmonella typhimurium* TA1535	urine of mice after a single oral dose of 1000 mg/kg		-	study from 1977, reported by Gar92
Ames	*Salmonella typhimurium* TA100, TA98	not reported	with and without RLiA with and without RLiA	+ -	study from 1979, reported by Gar92
Ames	*Salmonella typhimurium* TA1535, TA1538	- 2000 µg/plate	with RLiA without RLiA with RLiA without RLiA	±[b] - ± -	study from 1979, reported by Gar92
Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	not reported	with RLiA without RLiA	TA98: - TA100: - TA1538: - TA1535: + TA1537: + all: -	study from 1981, reported by Gar92
Ames	*Salmonella typhimurium* TA100, TA1535	not reported	with and without RLiA	+	study from 1982, reported by Gar92
Ames spot test	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	0.05 mg/plate and 10.0 mg/plate	with and without RLiA	-	Wad79
Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	0 - 10 mg/plate; TA 100: 0 - 1.0 mg/plate	with and without RLiA and HLiA[c]	TA98: - TA1537: - TA100: + TA1535: +	Can86
Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	range not specified	with and without RLiA	TA98: - TA1537: - TA100: + TA1535: +	Kie86
Ames	*Escherichia coli* WP2 uvrA	20 - 10,000 µM		+	Hem80
Ames	*Escherichia coli* WP2 or WP2 uvrA	not reported		-	study from 1981, reported by Gar92
induction of mitotic gene conversion	*Saccharomyces cerevisiae* ID1	not reported	with and without RLiA	+	study from 1982, reported by Gar92

[a] Rat liver activation.

[b] No dose response.

[c] Hamster liver activation.

Table 9 Continued.

type of test	species	concentrations tested	remarks	results	references
induction of UDS	human mononuclear white cells	up to 500 ppm		-	study from 1977, reported by Gar92
induction of gene mutation	mouse lymphoma cells	not reported	with without RLiA	- +	2 studies from 1982 and 1986, reported by Web93
chromosomal aberrations	rat liver cells	3.75 - 20 µg/ml		+	study from 1981, reported by Gar92
induction of single strand breaks in DNA	male and female Wistar rats	single oral dose of 500 mg/kg	test in liver DNA	-	study from 1981, reported by Gar92
induction of micronuclei	10 female $B6D2F_1$ mice	5 gavage doses of 1000 mg/kg		-	study from 1977, reported by Gar92
induction of neoplastic transformation	baby hamster kidney cells	up to twice the LC50		+	study from 1981, reported by Gar92
host-mediated assay	*S. typh.* inoculated into the peritoneal cavity of mice	mice pretreated by gavage for 5 days with 1000 mg/kg		-	study from 1977, reported by Gar92
dominant lethal assay	10 male $B6D2F_1$ mice	dermal treatment with 3000 mg/kg, three times per week, for a minimum of 8 weeks	males were mated with several virgin females; test on pregnancy, total number of implants and foetal death	-	study from 1977, reported by Gar92

0.02) reduction in the number of live foetuses per litter. Foetal toxicity was evident as statistically significantly ($p < 0.001$) dose related reductions of foetal body weight and crown-rump length (Har81). However, in view of the very toxic and for occupational circumstances irrelevant route of exposure the results will not be used in the risk assessment.

Female CD rats (200-275 g) were dosed by gavage with 0, 160, 320, 640, and 1280 mg/kg/day BPA dissolved in corn oil on gestation days (GD) 6 through 15. On the 20th day of gestation all rats were sacrificed and examined. Two replicate studies of the developmental toxicity evaluation were conducted. Approximately equal numbers of sperm-positive females were assigned to each of five dose groups in each replicate (>10 per dose per replicate) for a total of at least 20 confirmed-pregnant females per dose.

Dams in the high-dose group (1280 mg/kg/day) exhibited an unexpectedly high mortality rate of 26% (7/27 animals), 10% (1/10) in the first and 35% (6/17) in the second replicate. A mortality rate of 10% was predicted, based on a preliminary toxicity study. The authors have not found an explanation for this replicate-dependent increase of maternal mortality. There was no increase in the incidence or percentage of foetuses

malformed per litter in this group. Data from the 1280 mg/kg/day dose group are excluded from data used to make conclusions regarding the teratogenic potential of BPA.

The primary clinical signs associated with BPA treatment were lethargy, piloerection, pica, rough coat, wet urogenital area, weight loss, and alopecia. These effects occurred infrequently in control rats. Maternal toxicity of CD rats exposed to BPA is shown in Table 10. In the 27 to 29 treated rats in each dose group, pregnancy was confirmed in 92 to 100% of the treated females. No significant differences were observed among treatment groups with respect to the total of number of corpora lutea per dam, the number of implantation sites per dam, or the percentage of preimplantation loss (data not shown). Maternal weight gains (gestation, treatment and gestational corrected for gravid uterine weight) were reduced in a dose-related manner. Gravid uterine weight and absolute and relative maternal liver weight were unaffected by BPA treatment.

There was no significant effect of BPA treatment on any observed measure of developmental toxicity, including percentage resorptions per litter, percentage litters with resorptions, number of live foetuses per litter, sex ratio, average foetal body weight per litter, percentage malformed foetuses per litter, and percentage litters with malformed foetuses. It is concluded that BPA does not cause external, visceral, or skeletal malformations at dosages which caused significant maternal toxicity (Mor87, Geo85).

In a specific breeding study groups of ten male and ten female Charles River rats were fed 0, 1000, 3000, and 9000 ppm BPA in the diet for 17 weeks. It is not clear at what age of the rats the experiment started. At about 100 days of age the F_0 generation rats were mated one female with one male of the same dose level. Dietary feeding was maintained throughout the reproductive phase. After weaning selected offspring, 15 males and 15 females/group, were used for the 90-day feeding study. There were no compound-related changes in appearance or behavior. One control male and two females at each of the two top dose levels died in the F_1 generation. In the F_0 generation there were no effects in fertility indices, pups/litter or pup survival. Slight reductions in body weight gain at 21 days of age were observed at 3000 and 9000 ppm. In the F_1 90-day feeding study body weights were decreased in females at all dose levels and in males at 3000 and 9000 ppm. Haematology, biochemistry, urinalysis and ophthalmoscopy were all normal. No compound related gross lesions or variations in organ weights were observed in any rats from the experimental groups. It is concluded that fertility, the number of pups/litter and pup survival were not affected in rats by dietary feeding of BPA at levels up to 9000 ppm. Pup weights were reduced at 3000 and 9000 ppm. Parental body weights were also reduced at these dose levels. The only effects observed in the F_1 90-day study were reductions in food consumption and body weight (study from 1976, reported by Web90).

Table 10 Maternal toxicity in CD rats administered BPA by gavage on gestational days 6 through 15 (Mor87).

	BPA (mg/kg/day)			
	0	160	320	640
subjects (dams)				
total treated	27	27	27	29
removed	2[a]	0	1[b]	0
no. pregnant (%) at sacrifice	23 (92)[c]	26 (96)	24 (92)	29 (100)
maternal weight gain (g)[d]				
gestation period (GD 0-20)	122.2±4.4*	108.4±3.2**	106.2±3.4**	104.6±2.9**
treatment period (GD 6-15)	42.0±1.8*	27.2±2.3**	19.6±2.9**	19.4±2.4**
corrected weight gain[e]	50.3±2.5*	36.4±2.6**	37.4±2.1**	33.4±2.5**
gravid uterine weight[d]	71.9±3.7	72.0±2.5[f]	68.8±2.6	71.2±2.7
maternal liver weight[d]				
absolute (g)	15.4±0.1	14.5±0.2	15.0±0.3	14.7±0.3
relative (% body weight)	4.3±0.1	4.2±0.1	4.4±0.1	4.3±0.1

[a] One dam was removed due to punctured oesophagus; one dam was removed due to preexisting. Pathological conditions found at sacrifice including large bladder, calculi, and small left kidney.

[b] One dam received 1/2 the appropriate dose on GD 13, due to a malfunction of the gavage syringe, and was removed.

[c] One dam had all resorptions.

[d] Includes all dams pregnant at sacrifice; mean ± SE.

[e] Weight gain during gestation minus gravid uterine weight.

[f] One gravid uterine weight was not recorded.

* Linear trend test, $p < 0.05$.

** Dunett's test or William's test, $p < 0.05$.

The study was repeated using lower dose levels: 0, 100, 250, 500, 750 or 1000 ppm BPA in the diet. Since no effects were expected, based on the above study results, and were not found, only the final conclusion is given: the dietary feeding of BPA at levels up to 1000 ppm had no effect on male or female fertility for one generation and no effect on pup survival and growth. The F_1 feeding of doses up to 1000 ppm for 90 days had no meaningful toxicological effects (study from 1978, reported by Web90).

BPA, mice

Female CD-1 mice (20-35 g) were dosed by gavage with 0, 500, 750, 1000 and 1250 mg/kg/day BPA dissolved in corn oil on gestation days 6 through 15. On gestation day 17 mice were killed and examined. Like the study conducted on CD rats as described before two replicates were performed (>10 mice per dose group per replicate). Approximately equal numbers of mice were pregnant in each treatment group (Table 11). BPA treated females exhibited clinical signs of toxicity including arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss,

Table 11 Maternal toxicity in CD-1 mice administered BPA by gavage on gestational days 6 through 15 (Mor87).

	BPA (mg/kg/day)				
	0	500	750	1,000	1,250
subjects (dams)					
total treated	29	29	29	34	33
removed	0	1[a]	1[a]	2[b]	0
no. pregnant (%) at sacrifice	26 (90)	23 (88)	21 (78)	23 (77)	21 (78)
maternal weight gain (g)[c]					
gestation period (GD 0-17)	19.8±0.9*	21.8±1.2	20.7±1.0	18.1±1.6	13.5±2.1**
treatment period (GD 6-15)	11.6±0.4*	12.2±0.8	12.5±0.7	9.4±1.1	6.6±1.2**
corrected weight gain[d]	4.9±0.4	6.2±0.5	6.0±0.8	4.6±0.8	3.5±0.7
gravid uterine weight[c]	14.7±0.8*[e]	15.6±0.9	14.8±0.9[e]	13.4±1.2	10.0±1.5**
maternal liver weight[c]					
absolute (g)	2.6±0.0	3.0±0.1**[f]	3.1±0.1**	3.0±0.1**	2.8±0.1**
relative (% body weight)	5.4±0.1*	5.9±0.1**	6.1±0.1**	6.3±0.2**	6.8±0.2**

[a] One dam was removed due to punctured oesophagus.
[b] Two dams were removed due to delivery before scheduled sacrifice.
[c] Includes all dams pregnant at sacrifice; mean ± SE.
[d] Weight gain during gestation minus gravid uterine weight.
[e] Gravid uterine weight for one dam was inadvertently not recorded.
[f] One liver weight was incorrectly recorded and was not included.
* Linear trend test, $p < 0.05$.
** Dunett's test or William's test, $p < 0.05$.

and wheezing. Maternal deaths occurred in all BPA dose groups, reaching 18% in the 1250 mg/kg/day group. There was a trend towards reduced maternal weight gain during both gestation and treatment, with mice in the highest dose group gaining significantly less weight ($p<0.05$) than those in the control group. Corrected weight gain (weight gain during gestation minus gravid uterine weight) was not significantly different among dose groups. There was a trend towards reduced gravid uterine weight with increasing BPA dose; the mean high-dose weight was significantly less than that of the control group. The absolute maternal liver weight was significantly increased for the 500, 750, and 1000 mg/kg/day dose groups compared to the control group. The relative maternal liver weight was significantly increased in all BPA dosed groups.

There was no difference among treatment groups in the number of implantation sites per litter, but the number of corpora lutea per dam decreased in relation to increasing BPA dose. There was no effect on preimplantation loss. The percentage resorptions per litter increased in the two highest dose groups, with the 1250 mg/kg/day group significantly different from the control group. There were seven litters in the high dose groups that were totally resorbed. A dose-dependent decrease in average foetal body weight per litter was observed with increasing BPA dose; the 1250 mg/kg/day average foetal body weight was significantly less than that of the control group. There

was no significant effect of BPA on the number of live foetuses per litter, on the sex ratio, on the percentage malformed per litter or on the percentage litters with malformed foetuses. There were no significant treatment-related effects on any measure of teratogenic response. It is concluded that BPA had no effect on the incidence of external, visceral, or skeletal malformations at dosages that cause significant maternal mortality (Mor87).

A continuous breeding study on CD-1 mice treated with BPA was performed (Ree84). Mice received a suspension of 0, 25, 50 or 100 mg BPA in corn oil via subcutaneous Silastic implants. The control group consisted of 40 mice of each sex and treatment groups of 20 mice of each sex. Eleven-week old male and female CD-1 mice were exposed to BPA during a 7-day premating period, a 98-day cohabitation group (one male and one female per cage), and a 21-day segregation period. Newborn litters are evaluated and discarded. During the 18-week treatment period, BPA released from the Silastic implants was approximately 11.65 mg for the 25 mg dose group, 20.05 mg for the 100 mg dose group, and 38.60 mg for the 100 mg dose group. Several animals in each treatment group expelled their implant through cutaneous lesions that developed over the implant or through the original site of incision. When this occurred, a new implant containing the original amount of BPA was inserted. Pregnant females were allowed to deliver their litter prior to being anaesthetized and reimplanted. Several animals received subcutaneous Silastic implants on as many as four occasions. A total of two females (one in the control group and one in the 50 mg dose group) died during the study. Exposure to BPA had no effect on body weight, fertility, the number of litters per fertile pair, and weights of liver, brain, pituitary gland, and male and female reproductive organs in this study. Although a few reproductive parameters were significantly different among treatment groups, these differences were random in nature and appeared to be due to chance alone. Because the Silastic implants tended to be expelled and since they appeared to release too little BPA to cause generalized or reproductive toxicity this study was terminated and neither a crossover breeding study, nor a study on reproductive performance in the offspring, as required by the National Toxicology Program (NTP) protocol, were performed. Under the conditions of this study, BPA exerted no adverse effects on fertility or reproduction in male and female CD-1 mice (Ree84).

A complete reproduction and fertility assessment in CD-1 mice was performed (Ree85). Twenty mice of each sex were fed with 0.25, 0.5, or, 1.0% BPA in their feed, representing 437.5, 875.0, and 1750.0 mg/kg body weight. A vehicle control group consisted of 40 mice of each sex. All mice were 11 weeks of age at the outset of the trial. For the first week animals were housed by sex. Subsequently, mice were randomly paired and cohabited for 98 days, one breeding pair per cage. Thereafter, each mouse was separated for a period of 21 days. Continuous exposure to BPA during

these three periods had no effect on the proportion of breeding pairs able to produce at least one litter. The number of litters per pair was significantly reduced ($p < 0.05$ or 0.01) in the 0.5 and 1.0% dose groups, and these groups had a significantly depressed ($p < 0.01$) number of live pups per litter relative to the control group. The proportion of pups born alive was significantly depressed ($p < 0.01$) in the 1.0% BPA group relative to the control group. Live male pup weight ($p < 0.05$) and live pup weight for sexes combined was significantly elevated ($p < 0.05$ or 0.01) for the 0.5 and 1% BPA groups relative to control pairs, whereas live female pup weight was significantly elevated ($p < 0.01$) relative to controls only in the 0.5% BPA group. The absence of a live female pup weight in the 1% BPA group in spite of a mean value that was elevated above controls was most likely due to the variability of the data for this parameter in the treated group. When pup weight was adjusted for the number of dead and live per litter there was no longer any significant difference among dose groups, implying that the larger absolute live pup weights were due to the smaller litter size in the 0.5 and 1.0% BPA groups. Postpartum body weights of the highest dose females were significantly below ($p < 0.01$) those from the controls, indicating generalized maternal toxicity.

Because of the significant decrease in the number of litters per pair and in the number of pups per litter at doses of 0.5 and 1.0% BPA, a crossover mating trial was conducted in order to determine the affected sex. Three combinations of breeding pairs were evaluated: control male x control female; 1% BPA male x control female; control male x 1% BPA female. These pairs were cohabitated for seven days, during which no BPA was administered, and then separated. Then BPA treatment was reinstated. The production of detected matings and fertility were not significantly different among these three groups of mating pairs. The number of live pups per litter (sexes combined) was significantly less ($p < 0.05$) in pairs with a treated male than in control pairs. The number of pups, live male pups, and live female pups per litter was significantly less in pairs with a treated female than in control pairs ($p < 0.01$) and in pairs with treated males ($p < 0.05$). When pup weight was adjusted for the number of live and dead pups per litter, no statistical differences were apparent. The proportion of pups born alive, the sex of pups born alive, and postpartum weights of the treated females after the crossover mating were not statistically different from controls.

By now, F_0 male and female mice used in the mating trials were weighed and necropsied. Body weights for treated females (1% BPA) were significantly below ($p < 0.05$) the control group, and both male and female treated (1% BPA) mice exhibited significantly increased ($p < 0.01$) adjusted liver and kidney weight and histopathological evidence of treatment-related hepatic and renal toxicity. Hepatic lesions in male mice included centrilobular hepatocytomegaly, multifocal necrosis, and multinucleated giant hepatocytes. Female mice exhibited multifocal necrosis, and multinucleated giant

hepatocytes. Renal lesions observed in treated F_0 male mice included tubular cell nuclear variability and amplification of spontaneous tubular and interstitial lesions normally seen in these mice. In addition to exhibiting renal lesions similar to those observed in the F_0 male mice, treated F_0 female mice had large microcalculi in the cortical tubules, sometimes associated with effaced tubular epithelium, tubular regeneration and/or dilated tubules containing proteinaceous or slightly pigmented tubular casts. In general, hepatic lesions were more severe in male mice while renal lesions were more prevalent in female mice. Treated males also had significantly reduced ($p < 0.01$) adjusted seminal vesicle weight and significantly reduced ($p < 0.01$) sperm motility, but no evidence of pathological lesions of the tissue of the reproductive system.

The offspring obtained in the last 21 days of the continuous breeding study, the F_1 generation, did not exhibit significant differences in body weights at 21 days of age or at 74 ± 10 days of age between BPA-treated mice and controls, indicating normal growth of pups surviving to the lactational and postweaning periods. However, continuous administration to 1.0% BPA of the F_1 generation mice was lethal to 37.5% (18/148) compared to 6.3% (8/126), 3.8% (4/105), and 13.9% (11/79) lethality observed in samples of 0, 0.25, and 0.5% BPA-treated mice, respectively.

In order to assess the reproductive effects of BPA on the F_1 generations, litters were randomly selected at day 21, were housed by sex, and maintained on the same feed level as their parents. At 74 ± 10 days of age a male and a female from different litters within treatment groups were cohabited for seven days. The pairs were then separated and the females were allowed to deliver their litters. There were 20 pairs in the 0, 0.25, and 0.5% BPA group and 11 pairs in the 1% BPA group due to decreased viability of weanlings in this group. One female died in the 0.25% BPA group during this trial. F_1 mice were necropsied three weeks after the cohabitation period. No significant difference was observed in the reproductive performance of F_1 breeding pairs exposed to BPA as compared to controls. Postpartum weights for F_1 females after delivery of a single litter did not differ significantly among treatment groups. However, at necropsy, adjusted liver and kidney/adrenal weight of BPA-treated F_1 male and female mice were significantly higher ($p < 0.05$ or 0.01) than of control mice. At the lowest dose tested the relative liver weights were increased 6.7% and 5.9% for males and females, respectively, and the increase of the relative kidney weights was 15.7 and 12.5%, respectively. Both organs exhibited an increase in treatment-related lesions. Centrilobular hepatocytomegaly, multifocal hepatocellular necrosis, and multinucleated giant hepatocytes were observed in the livers of male mice of all three treated groups, but were not observed in control F_1 males. Hepatic lesions in F_1 females included multinucleated giant hepatocytes, and multifocal necrosis that occurred in a dose-related manner and with less severity than in treated male F_1 mice. Multifocal mineralization of hepatic cells was also observed in the females of the 1% BPA group.

Kidney lesions including cortical tubular dilatation, tubular casts, microcalculi, and mineralization of renal cells occurred in a dose-related manner in both F_1 male and female mice. Renal lesions tended to be more prominent in F_1 female than in F_1 male mice. Treated F_1 males also exhibited significantly reduced ($p < 0.05$ or 0.01) adjusted weight of reproductive organs at all three dose levels, indicating BPA toxicity, although there was no histopathological evidence of tissue lesions. Sperm assessment indicated a significant reduction ($p < 0.01$) in sperm motility in the 0.5% BPA group relative to controls.

The authors concluded that BPA was a reproductive toxicant that caused a reduction in the number of live pups born in the F_0 generation at the two highest doses, and reduced sperm motility and weight of some male reproductive organs in both the F_0 and the F_1 generations, and reduced postnatal survival of the F_1 generation. These effects were accompanied by significant hepatic and renal toxicity in the parental F_0 and F_1 animals. It is possible therefore, that some or all of the adverse effects on reproductive performance observed in this study may be secondary to the generalized toxicity of BPA (Ree85). The committee feels that there are insufficient data to make a definitive conclusion on the mode of action of BPA.

DGEBPA, rats and rabbits

A one-generation reproduction study in rats was conducted in which DGEBPA-based epoxy resin (Araldite GY250 or TK10490) was administered by gavage at doses of 0, 20, 60, 180 and 540 mg/kg. Oral administration of this resin to males for ten weeks and to females for two weeks prior to mating produced a lower mean body weight in males at 540 mg/kg/day, but did not affect mating performance, gestation period, or the ability of females to successfully rear their offspring to weaning. No treatment-related macroscopic changes, differences in mean organ weights or histologic changes in the reproductive or alimentary tracts (highest dose only) in either sex of the F_0 generation were observed (study from 1989, reported by Gar92).

The same compound, TK 10490, was administered to rats and rabbits throughout gestation. The purity of the compound is not given, but the density varies between 0.998 and 1.009 g/ml. The nominal dosages for rats were 60, 180 and 540 mg/kg/day, for rabbits 20, 60 and 180 mg/kg/day. The achieved dosages were for rats 5 - 16% below those intended, for rabbits they were 4 - 23% below those intended. The compound was administered by oral gavage, on GD 6 - 15 to rats, and on GD 7 - 19 to rabbits. The group size was 22 - 24 rats, and 15 - 17 rabbits.

Results of the rat study

Treatment with the high dose was associated with:

- post-dosing salivation in all animals generally for five days
- retarded weight gain during the dosing period.

Treatment with the mid dose was associated with:

- post-dosing salivation in occasional animals for one to four days.

At 60 mg/kg no adverse effects were detected in the parent female.

Litter parameters as assessed by mean values for litter size, pre- and post-implantation losses, litter and mean foetal weight were not adversely affected by treatment.

Treatment with TK 10490 had no adverse effect on the incidence of malformations, visceral and skeletal anomalities or skeletal variants (Smi88a).

Results of the rabbit study

Treatment with the high dose was associated with:

- anorexia and cold ears in approximately half of the animals during the dosing period
- reduced food consumption resulting in initial weight loss during the dosing period.

Treatment at 60 and 20 mg/kg/day did not produce any clear or consistent adverse effects on the parent female. Mean litter parameters at 180, 60 and 20 mg/kg/day were essentially similar to the controls, none of the differences from controls attained statistical significance ($p > 0.05$).

Treatment with TK 10490 showed no obvious adverse effect on embryonic and foetal development as assessed by overall incidences and types of malformations, visceral and skeletal anomalies (Smi88b).

It can be concluded that 180 mg/kg/day is a NOAEL for rats and that 60 mg/kg/day is a NOAEL for rabbits.

DGEBPA was applied daily to the clipped skin of pregnant New Zealand White rabbits for approximately six hours a day at dose levels of 30, 100, or 300 mg/kg/day, dissolved in polyethylene glycol 400 on days 6 through 18 of gestation. Control rabbits received polyethylene glycol alone. Each treatment group consisted of 26 animals. All rabbits were killed on day 28 of gestation. Dermal application produced a dose-related increase in erythema, exfoliation/fissuring, haemorrhage, and oedema at the site of application. No treatment-related effects on body weights, body weight gains, or liver weights of pregnant rabbits were observed. A summary of the reproductive parameters

and foetal observations made at the time of Cesarean section are presented in Table 12. External, visceral, and skeletal observations were performed on the foetuses, but no statistically significant increases in malformations or variations were observed in any treatment group when compared with the control group. A total of eight foetuses, scattered throughout the dose levels, exhibited malformations. Most of these malformations have also been observed at these low frequencies in historical control data of New Zealand White rabbits. Therefore, it can be concluded that no evidence of embryo or foetal toxicity or teratogenicity was observed at any dose level used in this study. Thus, the embryo/foetal no-observed effect level for dermally applied DGEBPA was 300 mg/kg/day, the maximum tolerated dose (Bre88).

Conclusion

After oral administration of BPA to rats and mice during gestation there was no significant effect on any observed measure of developmental toxicity, or on the incidence of external, visceral, or skeletal malformations at dosages which cause significant maternal toxicity (rats) or mortality (mice). In a complete reproduction and fertility assessment by continuous breeding in mice treated with 0.25, 0.5 or 1% BPA significant hepatic and renal toxicity of BPA is the primary cause of the reproductive effects.

Continuous oral administration of a low molecular weight DGEBPA-based resin to male and female rats did not induce teratogenic or embryotoxic effects in the offspring. After oral administration of a low molecular weight DGEBPA-based resin during gestation there was no significant effect on any observed measure of developmental toxicity, or on the incidence of teratogenic or embryotoxic effects in rats and rabbits at dosages which induce maternal toxicity (540 mg/kg/day for rats, 180 mg/kg/day for rabbits).

Dermal application of the maximum tolerated dose of DGEBPA (300 mg/kg/day, 6 hr/day) on days 6 through 18 of gestation had no effect on the reproductive performance of rabbits. No embryo or foetal toxicity or teratogenicity was observed.

7.1.7 Other studies

BPA has a weak oestrogenic activity; when compared to the human hormone oestradiol-17ß, the oestrogenic activity of BPA is approximately 1 : 2000 that of oestradiol for rat oestrogen receptors and approximately 1 : 5000 that of oestradiol for human progesterone receptors (Kri93).

In another study the oestrogenic activity of BPA was 1000-fold lower than that of oestradiol (Bro95).

Table 12 The effect of dermal application of DGEBPA on reproductive parameters in rabbits (Bres88).

	DGEBPA (mg/kg/day)			
	0	30	100	300
no. deaths/no. of females	1/26	0/26	0/26	0/26
pregnancies detected by stain	0/0	0/6	0/5	1/4
% pregnant	100	77[a]	81	86
no. of litters	23[b]	20	21	23[c]
corpora lutea per dam[d]	9 ± 2	10 ± 1	10 ± 2	10 ± 2
implantations per dam[d]	7 ± 3	7 ± 3	7 ± 3	7 ± 2
live foetuses per litter[d]	6 ± 3	7 ± 3	7 ± 3	6 ± 3
% implantations resorbed	14 (23/164)	4 (6/142)	6 (8/144)	14 (20/148)
foetal body weight (g)[e]	36.7 ± 5.3	35.7 ± 5.3	36.7 ± 5.5	36.9 ± 5.6
foetal sex ratio, M:F	50:50	40:60[a]	45:55	49:51

[a] Statistically different from control or a binomial distribution ($\alpha = 0.05$).

[b] Two females aborted their litters.

[c] Two litters completely resorbed.

[d] x ± SD.

[e] x of litter means ± SD.

A single sc injection of 0.25 mg (5.2 - 6.9 mg/kg) into immature rats increased the glycogen production of the uterus 18 h later (Bit70).

The committee feels that these data are too few to evaluate their meaning properly.

7.2 Observations in man

7.2.1 *Irritation and sensitization*

Irritation

Complaints about eye, nose, and throat irritation have been received from workers exposed to BPA dust at average (8-h TWA) atmospheric levels of 5 mg/m^3 (EPA85). However, no information is available on the clinical aspects of the complaints, the number of persons exposed, the number with and without complaints or the size distribution of the particles. However, available monitoring data from other sources indicate that BPA dust is readily available because of its respirable size. In two samples collected during packaging of flaked BPA less than respectively 30 and 14% of the BPA dust by weight was less than 10 μ in size. Plant area monitoring studies showed daily levels between 0.4 and 6.8 mg/m^3. It can be concluded that at least a part of the BPA dust is inhalable, and possibly also respirable.

On the other hand, another report states that eye and nose irritation was generally not seen until concentrations approached 15 mg/m^3 (it is not given whether this concentration was an 8 h TWA) (Row62). Also here, data are lacking on clinical spects

and numbers of persons. The irritation is described as nuisance irritation, and, therefore, has to be ascribed to inert dust, rather than to BPA toxicity.

Generated dusts of BPA, if inhaled, may produce irritation of the upper respiratory passages. Skin contact may also cause some mild irritation (Oom83).

Sensitization

Several case studies of allergies to BPA and DGEBPA are listed in Table 13. All cases reacted positively to the patch tests.

Allergic reactions to BPA and DGEBPA were investigated by patch testing workers, patients, or volunteers on many different occasions. Results are listed in Table 14.

The studies where the number of workers that are occupationally exposed to DGEBPA is given, are taken together; they comprise of (Jol87, Hol93, Pre86, Bru89, Suh83). Of a total of 3331 workers there were 274 persons with skin disorders. Upon patch testing of these persons 137 reacted positively to DGEBPA. That means that the frequency in which sensitization occurs is in the order of 4%. This is in line with other incidences of allergy.

Cross-sensitization

When tested in a group of six patients with a confirmed allergic contact dermatitis to epichlorohydrin no cross sensitization was found with BPA. In all cases the patch with 1% BPA scored negative after 48 and 72 h (Joo88a).

When tested in a group of 71 patients with occupational contact allergy for DGEBPA, no cross sensitization occurred with BPA. Patch tests were performed with 1% BPA and approximately 0.55% DGEBPA (Jol87).

On the other hand, two of eight patients with contact allergy to bisphenol F (isomer of dihydroxydiphenylmethane) were also allergic for BPA (Bru85).

Four non-atopic females with hypersensitivity to BPA, confirmed by a positive patch test (1% in ethanol), showed positive reactions to dimethyldi-(4-hydroxyphenyl)silane (1% in acetone) (Fre61).

Eighteen patients hypersensitive to diethylstilbestrol are also allergic to BPA (Fre60 and Fre62a).

Three patients with allergic contact dermatitis for bis-GMA (an epoxyacrylate) were also allergic to DGEBPA (Jol90).

Conclusion

BPA induces mild irritation in skin, eyes, nose and throat.

Even in selected groups of workers allergic reactions to BPA are only elicited in rare cases.

Cross sensitization has been described between BPA and bisphenol F, dimethyldi-(4-hydroxyphenyl)silane, and diethylstilbestrol.

DGEBPA is a skin sensitizer, the incidence in occupationally exposed workers is approximately 4%. In a few workers it can cause asthma.

Three patients with allergic contact dermatitis for bis-GMA were also allergic to DGEBPA.

7.2.2 *Acute toxicity (incidents)*

No data available.

7.2.3 *Short-/long-term exposure (accidental, controlled)*

No data available.

7.2.4 *Epidemiological studies*

A chromosome aberration test on peripheral lymphocytes of human beings was conducted on nine individuals (aged 30-66 years, median 45.4 years) occupationally exposed to epoxy resins for 5-16 years (median 6.5 years; Mit80). The average MW of the epoxy resin was < 900, the main oligomer was DGEBPA, the hardener used was of the aliphatic amine type. There was a well-developed protective program but intermittent contamination of the skin could not be prevented. A control group consisted of nine workers matched for sex and age who carried out metal-work in the same factory, but had not been occupationally exposed to epoxy compounds. However, the smoking habits of both groups were not recorded.

The frequency of chromosomal aberrations was analyzed in peripheral lymphocytes cultured for 72 h. From each individual 200 metaphases were analyzed. The frequency of sister-chromatid exchanges in PHA-stimulated lymphocytes was studied after 72.5 h incubation; 20 cells with 46 chromosomes were examined in each individual.

There was no difference between the controls and the group exposed to epoxy resin. This was true for all types of aberrations recorded, including the sister-chromatid exchanges. The results, however, should be interpreted with caution. It is generally

Table 13 Case studies of allergic reactions to BPA and DGEBPA.

exposure[a]	sex	age	symptoms	patch test	reference
epoxy resin (1 week)	man	18 yr	irritation on the wrist and forearms, dermatitis on the face and neck, oedema of the eyelids and external nares	1% BPA	Gau60
wax containing 15 or 30% BPA (5 yr)	man	53 yr	acute dermatitis of the right hand, a less florid dermatitis of his nose and nasolabial folds	1% BPA	Fre84
plastic footwear	woman	17 yr	dermatitis over the dorsa of both feet	1% BPA	Sri89
plastic footwear	man	25 yr	dermatitis over the dorsa of both feet	1% BPA	Sri89
epoxy resin (> 1 yr)	man	56 yr	contact dermatitis on the face, in the inguinal region, and on the lower legs	1% BPA	Joo90
probably glue used for repair of dental plates	woman	65 yr	burning mouth, burning tongue, slight erythema	BPA [?%] ICDRG-epoxy resin[b] [?%]	Joo88a, Joo88b
wool mixed with synthetic fibres (15 yr)	man	55 yr	petechial and purpuric lesions on the face and the dorsum of the fingers	1% BPA epoxy resin [?][c]	Rom81
door handles	woman	42 yr	dermatitis of the volar side of her hand	ICDRG-epoxy resin [?%]	Fre80
screwdrivers	man	not reported	hand eczema	ICDRG-epoxy resin [?%]	Fis87
metal under watch strap	woman	not reported	dermatitis under her watch strap	ICDRG-epoxy resin [?%]	Fre80
epoxy resin	man	53 yr	dermatitis on face, hands, arms and chest	ICDRG-epoxy resin [?%]; 0.1% DGEBPA	Bok82
epoxy resin	woman	27 yr	dermatitis on hands and face	5.8% epoxy resin; ICDRG-epoxy resin [?%]	Bok82
epoxy resin based green glue (four weeks)	woman	26 yr	dry fissured and itchy lesions on the finger tips of both hands and left palm	BPA [?%] epoxy resin [?][d]	Rom86

[a] Duration before beginning of the symptoms is presented in parentheses.

[b] ICDRG-epoxy resin is a commercial grade DGEBPA epoxy resin and has an average MW of 385 (Pre86). ICDRG = International Contact Dermatitis Research Group.

[c] Positive patch tests to colophy, formaldehyde, neomycin, 1% BPA, 5% urea-formaldehyde resin, 5% melamine formaldehyde, delayed response to epoxy resin.

[d] Standard patch tests were positive to epoxy resin, BPA, formaldehyde, paratertiarybutylphenol and formaldehyde resin. The green glue (1% and 0.1%) was positive in the patient and negative in 25 healthy controls.

Table 14 Patch tests performed on workers, patients, or volunteers.

group	patch test	result	reference
8 persons with dermatitis following occupational exposure to uncured epoxy resin, 6 positive patch tests to epoxy hardeners	1% BPA	no allergic reactions	Fre62b
50 control persons	1% BPA	no allergic reactions	Fre84
5 patients sensitive to epichlorohydrin	1% BPA	no allergic reactions	Joo90
100 patch-tested patients	1% BPA	no allergic reactions	Bru85
20 volunteers	1% and 2% BPA 1% DGEBPA	no allergic reactions	Pre86
236 workers with ACD[a] *not* caused by DGEBPA epoxy resins and 28 workers with current or past ACD caused by epoxy resins	1% BPA	1 allergic reaction	Jol90
13 persons with no occupational exposure to epoxy resins, but with a positive patch test to epoxy resin	1% BPA	7 allergic reactions	Fre62b
16 patients with contact dermatitis	1% BPA	6 allergic reactions, 1 photoallergic reaction	Gri81
50 control subjects	1% BPA	no allergic reactions	
48 persons sensitive to Epidian 5[b] of 422 working at 8 factories	2% BPA	13 allergic reactions	Kra76
8 workers (of 130 employees) with dermatitis, handling fibreglass coated with uncured epoxy resin (6/8 were tested)	1% BPA; 1% DGEBPA	all 6 had allergic reactions to DGEBPA; no allergic reaction to BPA	Hol89
71 workers with ACD caused by DGEBPA epoxy resins out of 1082 cases of occupational skin diseases among 2484 patients	1% BPA 1% epoxy resin (European standard) containing ± 0.55% DGEBPA	68 allergic reactions to DGEBPA; no allergic reactions to BPA	Jol87
167 individuals with a history suggestive of DGEBPA-based epoxy resin contact dermatitis, in this group 70 individuals with ACD	1% DGEBPA 1% BPA	30 allergic reactions to DGEBPA; no allergic reactions to BPA; 19 allergic reactions to different types of hardeners	Hol93
8 workers exposed to dense fumes of heated epoxy resin, consisting of 88.5% BPA	1% epoxy resin (88.5% BPA); 0.001-1% epoxy resin and 0.01-1% BPA followed by UV-A (6 J/cm^2)	3 allergic and 4 photoallergic reactions to epoxy resin; 8 photoallergic reactions to BPA	All79
8 healthy volunteers	1% epoxy resin (88.5% BPA) and 1% BPA followed by UV-A (20 J/cm^2)	no photoallergic reactions	All79

Table 14 Continued.

group	patch test	result	reference
19 of 26 workers with work-related eruptions in an epoxy resin manufacturing plant with 228 workers	1% ICDRG epoxy resin[c] (average MW 385); 1% liquid epoxy resin (average MW 370) 1% solid epoxy resin (average MW 980, containing 10-15% DGEBPA); 1% epichlorohydrin 1% and 2% BPA	10 allergic reactions to ICDRG epoxy resin, 8 to liquid epoxy resin, 7 to solid epoxy resin, and 7 to all 3 types; 8 allergic reactions to epichlorohydrin; 4 concomitant sensitizations to epoxy resin; no allergic reactions to BPA	Pre86
1559 patients	1% DGEBPA	58 allergic reactions	Hol93
5 spinners in a fibre glass industry in contact with non-hardened epoxy resin, 1 worker in contact with dry glass fibre some of which epoxy coated	DGEBPA [?%]	6 allergic reactions	Dah79
1008 workers with ACD or other skin diseases *not* caused by DGEBPA epoxy resins out of 2484 patients	1% epoxy resin (European standard) containing ± 0.55% DGEBPA	15 allergic reactions	Jol87
6 workers with ACD caused by DGEBPA epoxy resins with a MW>700 out of 2484 patients	1% epoxy resin (European standard) [DGEBPA concentration not reported, probably ± 0.55%]	6 allergic reactions	Jol87
34 patients suspected for occupational contact dermatitis	1% DGEBPA	34 allergic reactions	Fre77
8 patients suspected for occupational dermatitis to a commercial epoxy resin with average MWs of 1280 and 1850	3.7% average MW 1280 5.3% average MW 1850	8 allergic reactions caused by DGEBPA present in the resin	Fre77
23 workers with ACD caused by DGEBPA epoxy resins	1% DGEBPA	23 allergic reactions[g]	Jol90
5 workers with a past relevant ACD caused by DGEBPA epoxy resins	1% DGEBPA	5 allergic reactions	Jol90
7 workers with ACD and 1 worker with contact urticaria mainly caused by the hardeners or the diluents present in DGEBPA epoxy resins	1% DGEBPA	1 allergic reaction	Jol90
66 spinners working in the glassfibre industry	1% DGEBPA-based epoxy resin [average MW not reported]	16 allergic reactions	Cuy75
79 workers (of a total of 159 employees) making printed circuit boards with a.o. DGEBPA, with current or previous allergic or irritant skin disorders	dust extract[d] DGEBPA [concentration not reported]	6 allergic reactions to dust extract and DGEBPA	Bru89
79 age and sex matched controls	DGEBPA [concentration not reported]	3 allergic reactions	Bru89

Table 14 Continued.

group	patch test	result	reference
135 workers handling uncured epoxy resin employed by 10 companies in the construction industry	1% epoxy resin (European standard) [concentration DGEBPA or average MW not reported]	25 allergic reactions	Put84
871 patients suspected for ACD	1% ICDRG-epoxy resin[c] (average MW 385)	3 allergic reactions	Pre86
35 workers in a ski-stick factory with 293 employees	1% ICDRG-epoxy resin[c] (average MW 385)	15 allergic reactions[e]	Suh83
20 unexposed controls and 5 exposed patients	prick test with epoxy resin containing 89% DGEBPA	no allergic reactions	Kan91
23 workers making DGEBPA epoxy resins with allergic and irritant skin disorders of a total of 74 employees	1% Epidian 5[b] 1% Epidian 3[f]	5 allergic and 9 photoallergic reactions to Epidian 5; 2 allergic and 6 photoallergic reactions to Epidian 3	Bac88
22 control persons	1% Epidian 3 1% Epidian 5	no allergic or photoallergic reactions	Bac88
99 persons in contact with epoxy resins and with dermatitis	1% Epidian 5[b]	48 allergic reactions	Kra76

[a] ACD: allergic contact dermatitis.

[b] CAS reg. nr. 25068-38-6, a polymer from BPA and epichlorohydrin.

[c] ICDRG = International Contact Dermatitis Research Group

[d] Dust collected from the area around the impregnation machines, extracted with ethanol and adjusted to a DGEBPA concentration of 1%.

[e] One of them had an immediate urticarial reaction, he had both dermatitis and rhinitis.

[f] CAS reg. nr. not known, probably the same polymer as Epidian 5 with a different average MW.

[g] two of these patients (further described by Kan91) had occupational immediate allergy (asthma) and delayed allergy (allergic contact dermatitis). Both reacted to the intracutaneous prick test and the specific IgE determinations. A provocation test was not performed.

agreed that 48-52 h cultures will issue first-division cells, 72 h will give first, second and third divisions. The use of a 72-h-fixation time for the assay of chromosomal aberrations may therefore result in a loss of cells with aberrations. It should also be mentioned that only G_0 cells are assayed in peripheral blood investigation, cells in other stages of the cycle may be more sensitive. Another important factor may be the type of exposure. The people in this study were exposed by skin contact, but probably not by inhalation as the epoxy resin has a low vapour pressure (Mit80). However, dermal absorption in mice is slow (section 5.1) and it may be expected that this is the same for humans. It was stated that it cannot be excluded that if individuals are exposed by inhalation they will receive higher doses, which may raise the level of chromosomal aberrations above normal. But due to the expected low vapour pressure of DGEBPA,

workers can only be exposed to high concentrations of DGEBPA after aerosol formation or if the material is heated.

A health-hazard evaluation was performed at a manufacturing site using DGEBPA-based epoxy resin (study from 1975, reported by Gar92). Based on the results of environmental air measurements, medical questionnaires, pulmonary function tests, and skin patch tests, it was concluded that the resin used did not represent a health hazard at the concentrations measured during normal operating conditions. The concentrations were not given.

Conclusion

No chromosomal aberrations, including sister-chromatid exchanges were seen in workers occupationally exposed to DGEBPA.

7.3 Summary

7.3.1 Bisphenol A

Animal data

BPA is a slight skin irritant.

BPA is not a skin sensitizer in guinea pigs. BPA is a photosensitizer in mice, but not in guinea pigs.

According to EC classification based on LD_{50} data, BPA is of a low order of toxicity after oral and dermal administration. Due to the low vapour pressure of BPA, and the lack of data, the inhalation toxicity cannot be assessed.

Subcutaneous implantation of BPA had no effects on mice in dosages up to 100 mg.

Oral dosing via the diet of 5% BPA for two weeks killed six out of eight mice. At 2.5% BPA mice showed dehydration, dyspnoea, lethargy, tremors, and ptosis. Feeding of 15,000 to 25,000 ppm for 13 weeks depressed weight gain in male mice. In female mice weight gain was depressed after feeding BPA from 5000 ppm upward, but the decrease was not dose-related. Multinucleated giant hepatocytes were observed in male mice after feeding BPA from 5000 ppm with a dose-related increase in incidence and severity.

In rats 8000 - 12,000 ppm BPA in the diet reduced body weight gain after two, four and eight weeks. Feeding rats 2500 ppm BPA for 90 days induced slight alopecia. Enlarged caeca were observed after feeding from 500 ppm upward in female rats and

from 250 ppm upward in males. No microscopic abnormalities were found. Hyaline masses were found in the bladder of male rats, there was no dose-related increase.

Feeding dogs for 90 days with 9000 ppm BPA increased the mean liver weight. No other changes were observed. No effects were observed after feeding 3000 ppm.

The almost maximum attainable concentration in air, 150 mg/m^3, and 50 mg/m^3, induced porphyrin-like reddish staining around the nose, and perineal soiling in rats, decreased body weight, and very slight to slight hyperplasia and chronic inflammation in the nasal cavity. The effects were reversible upon cessation of exposure. The 90-day no-effect level for rats was 10 mg/m^3.

There is no convincing evidence that BPA is carcinogenic for rats or mice of either sex. The lowest dose tested, 74 mg/kg/day, reduced the body weight gain in male and female rats. The latter were more sensitive to this effect.

BPA does not induce mutations in bacteria, does not induce chromosomal aberrations, sister chromatid exchanges, or transformation in mammalian cells *in vitro*.

After oral administration of BPA to rats and mice during gestation there is no significant effect on any observed measure of developmental toxicity, or on the incidence of external, visceral, or skeletal malformations at dosages which cause significant maternal toxicity (rats) or mortality (mice).

In a complete reproduction and fertility assessment by continuous breeding in mice treated with 0.25, 0.5, or 1% BPA, significant hepatic and renal toxicity of BPA occurs simultaneously with reproductive effects.

Human data

BPA induces mild irritation in skin, eyes, nose and throat.

Even in selected groups of workers allergic reactions to BPA are only elicited in rare cases. Cross sensitization has been described between BPA and bisphenol F, dimethyldi-(4-hydroxyphenyl)silane, and diethylstilbestrol.

7.3.2 *Diglycidyl ether of bisphenol A*

Animal data

DGEBPA is a skin irritant. It is either not or at most only a slight eye irritant. DGEBPA is a strong skin sensitizer.

According to EC classification based on LD_{50} data, DGEBPA is of a low order of acute toxicity upon oral and dermal administration. Due to the low vapour pressure of DGEBPA and the lack of data, the acute inhalation toxicity cannot be assessed.

The feeding of DGEBPA to rats at dietary concentrations up to 30,000 ppm for three months does not induce systemic toxicity. Dosages of 50,000 ppm induce death in 100% of the rats by the end of 20 weeks, mainly due to malnutrition.

After dermal application and subcutaneous injections of pure and commercial DGEBPA no skin tumours developed in rats and mice. Although lymphoreticular tumours were increased in some groups of some experiments, the data lacked consistency and therefore the increase of this spontaneously occurring tumour is not considered indicative of a carcinogenic potential of the compound.

DGEBPA is mutagenic in bacterial test systems. It probably causes basepair substitutions rather than frameshift mutations. In higher concentrations (0.8 mg/mouse) DGEBPA or a metabolite (glycidaldehyde) may react with DNA in mammals *in vivo* after dermal application.

DGEBPA may induce neoplastic transformations, gene mutations and chromosomal aberrations in mammalian cells *in vitro*. It is negative in the host-mediated assay. It does not induce UDS in human cells *in vitro*. No induction of micronuclei, dominant lethality or DNA single strand breaks are observed in mammals *in vivo*.

Continuous oral administration of commercial DGEBPA to male and female rats did not induce teratogenic or embryotoxic effects in the offspring. After oral administration of commercial DGEBPA during gestation, there is no significant effect on any observed measure of developmental toxicity, or on the incidence of teratogenic or embryotoxic effects in rats and rabbits at dosages which induce maternal toxicity (540 mg/kg/day for rats, 180 mg/kg/day for rabbits). Dermal application of the maximum tolerated dose of DGEBPA (300 mg/kg/day, 6 h/day) on days 6 through 18 of gestation had no effect on the reproductive performance of rabbits. No embryo or foetal toxicity or teratogenicity was observed.

Human data

DGEBPA is a skin sensitizer, the incidence in occupationally exposed workers is approximately 4%. In a few workers it can cause asthma.

Three patients with allergic contact dermatitis for bis-GMA were also allergic to DGEBPA.

No chromosomal aberrations, including sister-chromatid exchanges were seen in workers occupationally exposed to DGEBPA.

Chapter 8

Evaluation of human health risk

8.1 Groups at extra risk

Because of the sensitizing properties of DGEBPA workers who have developed a DGEBPA allergy are at extra risk.

8.2 Assessment of health risk

8.2.1 Bisphenol A

Systemic effects

There are insufficient human data upon which to base the risk assessment. The point of departure is therefore the animal data.

In a long-term oral study BPA was found not to be carcinogenic in male and female rats and mice. Neither were reproductive effects found in several studies with rats and mice. The critical effect of BPA is considered to be the reduced body weight gain followed by toxicity in liver and kidneys. The evidence can be found in several studies (NTP82, Ree85, Mor87).

Point of departure is the 13-week inhalation study with intermittent exposure to rats (study from 1988, reported by Web90). The critical effect was the slight to very slight nasal hyperplasia and inflammation at 50 and 150 mg/m^3, which was fully reversible within 12 weeks after cessation of exposure. The NOAEL was 10 mg/m^3. In

view of the absence of systemic effects, and the fact that the margin of safety for local effects between the NOAEL and the LOAEL is a factor 5, and the fact that rats are obligatory nose-breathers and man is not, the committee concludes that for extrapolation to humans a safety factor is not necessary. In view of the low vapour pressure of BPA this concentration can only be present in the air as solid particles. Furthermore, the particle size can be smaller than 10 μ (see section 7.2.1), which implies that BPA dust is inhalable, and partly respirable. For inhalable and respirable dust the present Maximum Allowed Concentration-values are 10 mg/m^3 and 5 mg/m^3, respectively. The committee recommends to use these values as occupational exposure limits for BPA.

Local effects

BPA is a slight skin irritant in animals. In humans it is a mild skin, eye, nose and throat irritant. It is not a skin sensitizer.

8.2.2 *Diglycidyl ether of bisphenol A*

Systemic effects

There are insufficient human data upon which to base the risk assessment. The point of departure is therefore the animal data.

DGEBPA is not carcinogenic in male and female mice after dermal application and subcutaneous injections in several long-term studies. In rats it induced sarcomas at the injection site but there was no systemic carcinogenicity. After oral administration to rats and rabbits and after dermal application to rabbits no embryo or foetal toxicity or teratogenicity was observed.

The critical effect of DGEBPA is considered to be the reduced body weight gain found in male rats after oral administration of 540 mg/kg/day for ten weeks; maternal toxicity was observed in pregnant rats after oral administration of 540 mg/kg/day during gestation and in pregnant rabbits after oral administration of 180 mg/kg/day during gestation. In all three cases a commercial DGEBPA-based epoxy resin was used (Araldite GY250 or TK 10490). The maternal toxicity is limited to post-dosing salivation and retarded weight gain during the dosing period in rats, and anorexia, cold ears and reduced food consumption during the dosing period in rabbits. The treatment was not associated with adverse embryonic or foetal effects. The dose of 180 mg/kg/day appears to be a NOAEL for rats. The dose of 60 mg/kg/day is a NOAEL for rabbits (Smi88a, Smi88b).

To extrapolate from animals to man a safety factor of 10 is used. Using the lowest NOAEL found and assuming the weight of a human to be 70 kg, this results in (70 x

60) : 10 mg/day = 420 mg/day. Assuming that this amount is absorbed during an 8 hours working day, that 10 m^3 of air is inhaled during an 8 h shift, and that absorption is 100%, then a concentration of 42 mg/m^3 can be recommended as a health based occupational exposure limit. In view of the expected low vapour pressure of DGEBPA this concentration can only be present in the air as solid particles. In the Netherlands the Maximum Allowed Concentration for respirable dust is 5 mg/m^3 and for inhalable dust 10 mg/m^3. The committee recommends to use these values as occupational exposure limits for DGEBPA.

Local effects

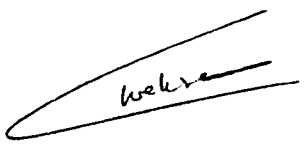
DGEBPA is a skin irritant and a skin sensitizer. The incidence of sensitization for occupationally exposed workers is approximately 4%. It is not or at most a slight eye irritant.

8.3 Recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends an occupational exposure limit of 10 mg/m^3 for bisphenol A and for bisphenol A diglycidylether in the form of inhalable dust and of 5 mg/m^3 for these compunds in the form of respirable dust as an 8 h Time-Weighted Average Concentration.

In order to prevent sensitization skin contact with bisphenol A-diglycidylether should be avoided.

Rijswijk, 12 September 1996,
On behalf of the committee



mrs ir C Hoeksema,
scientific secretary

Dr VJ Feron,
chairman

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Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in

the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committee

- VJ Feron, *chairman*
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- RB Beems
  toxicologic pathologist; National Institute of Public Health and Environmental Protection, Bilthoven
- DJJ Heederik
  epidemiologist; Wageningen Agricultural University
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- PTh Henderson
  professor of toxicology; University Limburg, Maastricht
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- G de Mik
  toxicologist; National Institute of Public Health and Environmental Protection, Bilthoven
- J Molier-Bloot
  occupational physician; Academic Medical Centre (AMC), Amsterdam
- PC Noordam, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sports, Rijswijk

- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol
- GMH Swaen
  epidemiologist; University Limburg, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- AAE Wibowo
  toxicologist; Coronel Laboratory, Amsterdam
- F de Wit
  occupational physician; Labour Inspectorate, Deventer
- C Hoeksema, *secretary*
  Health Council of the Netherlands, Rijswijk
- CA Bouwman, *secretary*
  Health Council of the Netherlands, Rijswijk

The first draft of the present advisory report was prepared by drs MA Maclaine Pont, from the Wageningen Agricultural University, by contract with the Netherlands Ministry of Social Affairs and Employment.

Secretarial assistance was provided by mrs Y Meems-von Schmidt.
Lay-out: J van Kan.

Annex C

Comments on the public review draft

A draft of the present report was released in 1994/1995 for public review. The following organisations and persons have commented on the draft document:

- dr JI Delic
  Toxicology unit, Health and Safety Executive, England
- dr WF Tordoir
  Shell International Petroleum Maatschappij BV, The Netherlands

Annex **D**

Synonyms of bisphenol A

2,2-(4,4'-dihydroxydiphenyl)propane
2,2-bis(4-hydroxyphenyl)propane
2,2-bis(p-hydroxyphenyl)propane
2,2-bis-4'-hydroxyfenylpropan
2,2-di(4-hydroxyphenyl)propane
2,2-di(4-phenylol)propane
4,4'-(1-methylethylidene)bisphenol
4,4'-bisphenol A
4,4'-dihydroxy-2,2-diphenylpropane
4,4'-dihydroxydiphenyl-2,2-propane
4,4'-dihydroxydiphenyldimethylmethane
4,4'-dihydroxydiphenylpropane
4,4'-dimethylidenediphenol
4,4'-isopropylidenebisphenol
4,4'-isopropylidenediphenol
bis(4-hydroxyphenyl)propane
bis(4-hydroxyphenyl)dimethylmethane
bis(p-hydroxyphenyl)propane
bisphenol
bispherol A
dian
dimethyl-bis(p-hydroxyphenyl)methane

dimethylmethylene-p,p'-diphenol
diphenylolpropane
DPP
NCI-C50635
Ipognox 88
isopropylidene-bis(4-hydroxybenzene)
Parabis A
Plucarol 245
p,p'-dihydroxydiphenyldimethylmethane
p,p'-dihydroxydiphenylpropane
p,p'-isopropylidenebisphenol
p,p'-isopropylidenediphenol
Rikabanol
ß-di-p-hydroxyphenylpropane
ß,ß'-bis(p-hydroxyphenyl)propane

Annex **E**

Synonyms of the diglycidylether of bisphenol A

2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane
2,2-bis(4-hydroxyphenyl)propane diglycidyl ether
2,2-bis[p-(2,3-epoxypropoxy)phenyl]-propane
2,2-bis(p-glycidyloxyphenyl)propane
2,2-bis(4-glycidyloxyphenyl)propane
2,2-bis(p-glycidyloxyphenyl)dimethylmethane
2,2-bis(p-hydroxyphenyl)propane diglycidyl ether
4,4'-bis(2,3-epoxypropoxy)-diphenyldimethylmethane
4,4'-dihydroxydiphenyldimethylmethane diglycidyl ether
4,4'-isopropylidenebis[1-(2,3-epoxypropoxy)benzene]
4,4'-isopropylidenediphenol diglycidyl ether
4,4'-isopropylidenediphenol-epichlorohydrin resin
Araldite GY250
Araldite GY6010
Araldite 6005
bis(4-glycidyloxyphenyl)dimethylmethane
bis(4-hydroxyphenyl)dimethylmethane diglycidyl ether
bisphenol A diglycidyl ether
bisphenol A-epichlorohydrin condensate
BPADGE
BPDGE
D.E.R. 331 epoxy resin

dian diglycidyl ether
dian-bis-glycidylether
diglycidyl bisphenol A
diglycidyl bisphenol A ether
diglycidyl diphenylpropane ether
diglycidyl ether of 2,2-bis(4-hydroxyphenyl)propane
diglycidyl ether of 4,4'-isopropylidenediphenol
diglycidyl ether of 2,2-bis(p-hydroxyphenyl)propane
diomethane diglycidyl ether
Epikote 828
EPI-REZ 508
EPI-REZ 510
EPON 828
EPON resin 828
EPOTUF 37-140
epoxide A
epoxy resin B1
ERL-2774
GY 6010
OHSO3222
oligomer 340
p,p'-dihydroxydiphenyldimethylmethane diglycidyl ether

Annex **F**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at which inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion $(v/v)10^{-9}$
ppm	parts per million $(v/v)10^{-6}$
RD_{50}	dose at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit
STEL	short term exposure limit

tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental and Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Association (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAlvC	minimal alveolar concentration
MFO	mixed function oxidase

NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

BPA	bisphenol A
DGEBPA	diglycidylether of bisphenol A
MOAEL	minimal observed adverse effects level

Annex **G**

DECOS-documents

DECOS has produced documents on the following substances.

To be ordered from the Health Council of the Netherlands:

Acetone cyanohydrin	1995/05WGD
Butanol (1,2- and t-)	1994/10
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
Ethylene glycol ethers	1996/01WGD
Formamide and dimethylformamide	1995/08WGD
Man made mineral fibers	1995/02WGD
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
Propanol (1- and 2-)	1994/24
Thrichloroethane (-1,1,1)	1995/03WGD
Trichloropropane (1,2,3-)	1994/25

The following documents, that were published before 1994, can be ordered from the Sdu Uitgeverij Den Haag.

Acetaldehyde	RA 6/92
Acrylaten	RA 13/87

Aflatoxine B1, B2, G1 en G2	RA 6/87
Allylglycidylether	RA 1/92
Amyl acetate	RA 4/90
Aniline	RA 2/89
Anorganisch Lood	RA 2/80
Anorganische Kwikzouten	RA 3/82
Arc welding fume particles not containing chromium and nikkel	RA 1/93
Arseenverbindingen (anorganische)	RA 2/84
Asbest	RA 1/84
Asbest, Evaluatie van risico op kanker bij beroepshalve blootstelling aan (aanvullend op RA 1/84)	RA 9/89
Benzeen	RA 5/89
Beryllium and beryllium compounds	RA 4/88
Blootstelling, Gezondheidskundige aspecten van het begrip en van het meten/schatten ervan	RA 8/90
Butadiene (1,3-)	RA 5/90
Cadmium	RA 5/80
Caprolactam	RA 4/84
Carbon monoxide	RA 7/92
Carbonylfluoride and PTFE pyrolysis products	RA 3/88
Carcinogene stoffen	RA 3/80
Chloor	RA 6/80
Chloroform	RA 7/87
ß-Chloroprene	RA 4/93
Chroom en chroomverbindingen	RA 6/85
Cyclohexane	RA 15/90
Cyclohexanol	RA 3/90
Cyclohexanone	RA 9/93
Dibroomethaan	RA 5/87
Dichloorethaan (1,1-)	RA 8/87
Diisocyanates	RA 3/91
Dimethyl- en diethylsulfaat	RA 12/90
Dimethylamine	RA 10/90
Dimethylbutane (2,2- & 2,3-)	RA 7/93
Dimethylhydrazine	RA 2/87
Dinitro-*ortho*-cresol (4,6-)	RA 4/87
Dioxaan (1,4-)	RA 1/87
Epichloorhydrine	RA 1/86
Ethylacrylate	RA 6/90
Ethylacetate	RA 10/91
Ethyl Methanesulphonate (EMS)	RA 4/89
Ethylamine	RA 7/90
Ethylbenzene	RA 9/91
Ethyleenoxide	RA 6/89
Fenylhydrazine	RA 2/87
Fluorcarbons (except FC11)	RA 15/87
Fluorine compounds (inorganic)	RA 1/89
Fluorine	RA 1/89

Formaldehyde	RA 3/87
Fosfine	RA 1/80
Fijn hinderlijk stof; gezondheidskundige aspecten van bijlage 3 bij de Nationale MAC-lijst 1989	RA 9/90
Gasoline	RA 3/92
Heptaan (n-)	RA 1/81
Heptane (n-)	RA 6/93
Hexaan (n-)	RA 11/87
Hexachlorobenzene	RA 2/88
Hexanone (2-)	RA 2/90
Hydrazine	RA 2/87
Hydrogenfluoride	RA 1/89
Hydroxyethylhydrazine	RA 12/87
Isopropylglycidylether	RA 1/92
Isopropoxyethanol (2-)	RA 2/87
Koolmonoxide (Carbon monoxide)	RA 2/79 (7/92)
Kwikalkylverbindingen - Korte keten	RA 5/82
Kwikverbindingen (Organische)	RA 4/82
Lachgas (Nitrous oxide)	RA 2/85 (2/92)
Lasrook (Arc welding fume.....nickel)	RA 1/93
Mangaan	RA 1/82
Metallisch Kwik	RA 5/81
1-Methoxypropanol-2	RA 5/93
2-Methoxypropanol-1	RA 5/93
1-Methoxypropylacetate-2	RA 5/93
2-Methoxypropylacetate-1	RA 5/93
Methylacrylate	RA 1/90
Methyleenchloride (Methylene chloride)	RA 1/83 (8/92)
Methyl ethyl ketone	RA 16/90
Methyl isobutyl ketone	RA 4/91
Methyl Methanesulphonate (MMS)	RA 4/89
Methylbromide	RA 13/90
Methylpentane (2- & 3-)	RA 7/93
Monochloorethaan	RA 2/82
Monoketones (7/8 carbon chain aliphatic)	RA 14/90
Nikkel en nikkelverbindingen	RA 3/85
Nitropropaan (2-)	RA 1/85
Nitrous oxide	RA 2/92
Ozone	RA 4/92
para-Dichloorbenzeen	RA 1/88
Pentaan	RA 2/81
Phthalate esters	RA 8/93
Phthalic anhydride	RA 3/89
Piperazine	RA 7/91
Polyvinyl chloride (PVC) dust	RA 2/93
Propoxyethanol (2-)	RA 12/87
Propoxyethylacetate (2-)	RA 12/87
Pyridine	RA 3/93

Selenium en -verbindingen	RA 7/89
Silicon dioxide, crystalline forms of	RA 5/92
Stikstofdioxide (Nitrogen dioxide)	RA 5/85
Styreen	RA 8/89
Talc dusts	RA 6/91
Tetrahydrofuran	RA 1/91
Thiourea	RA 11/90
Tolueen diisocyanaat	RA 4/80
Tolueen	RA 2/91
Trichloorethaan (1, 1, 1-)	RA 3/81
Trichloorethyleen	RA 3/83
Trichlorofluoromethane	RA 14/87
Triethylamine	RA 2/83
Trimethylamine	RA 9/87
Vadiummetaal en anorganische verbindingen	RA 10/87
Wood dust	RA 8/91
Xylene	RA 5/91
Zwaveldioxide (sulphur dioxide)	RA 4/85