# Hydrogenated Terphenyl

Health-based recommendation on occupational exposure limits

To: the State Secretary of Social Affairs and Employment
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Health Council of the Netherlands

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# samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad een gezondheidskundige advieswaarde afgeleid voor de beroepsmatige blootstelling aan gehydrogeneerd terfenyl.
Dit advies is tot stand gekomen in de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS). Op www.gezondheidsraad.nl staat informatie over de taken van deze vaste commissie van de Gezondheidsraad.
De samenstelling van de commissie is te vinden op de laatste pagina van dit advies.

**Gebruik van gehydrogeneerd terfenyl**
Gehydrogeneerd terfenyl heeft een toepassing als thermische vloeistof die voornamelijk in installaties gebruikt wordt om warmte of koeling over te dragen. De stof wordt ook gebruikt als drager voor textielkleurstof en als weekmaker.
In de Europese Unie wordt jaarlijks meer dan 1.000.000 kilogram gehydrogeneerd terfenyl geproduceerd. Gehydrogeneerd terfenyl is niet of nauwelijks afbreekbaar in het mileu.

**Nadelige gezondheidseffecten**
In de literatuur zijn meldingen van huidirritatie, hoofdpijn en keelpijn van mensen die op hun werk per ongeluk met gehydrogeneerd terfenyl in aanraking kwamen (accidentele blootstelling). Verder is er weinig informatie beschikbaar over de relatie tussen blootstelling aan verschillende concentraties van deze stof en gezondheidseffecten bij mensen. Bij proefdieren kan langdurige blootstelling aan gehydrogeneerd terfenyl leiden tot een toename in orgaangewichten, waaronder de lever, en een afname van het lichaamsgewicht.

**Gezondheidskundige advieswaarde**
Voor schadelijke stoffen waaraan mensen tijdens hun werk kunnen worden blootgesteld, gaat de commissie GBBS na of er uit wetenschappelijk onderzoek een gezondheidskundige advieswaarde is af te leiden op basis van een veilige ondergrens. Met een veilige ondergrens wordt bedoeld: een blootstellingsniveau waarbij geen nadelige gezondheidseffecten te verwachten zijn. Op basis van de gezondheidskundige advieswaarde van de commissie kan de staatssecretaris een grenswaarde voor beroepsmatige blootstelling vaststellen.

**Geraadpleegde onderzoeken**
De commissie heeft de beschikbare onderzoeken naar het optreden van schadelijke gezondheidseffecten door blootstelling aan gehydrogeneerd terfenyl beoordeeld.
Het dierexperimenteel onderzoek van Farr et al. (1989) geeft de meest duidelijke relatie weer tussen blootstelling aan gehydrogeneerd terfenyl en gezondheidseffecten. In twee verschillende onderzoeken zijn ratten her-

haaldelijk aan gehydrogeneerd terfenyl blootgesteld via twee verschillende toedienings-routes (oraal of via inhalatie). Nadelige gezond-heidseffecten die optraden bij toenemende blootstelling waren toename in orgaangewichten en afname in lichaamsgewicht. Histopathologisch onderzoek vertoonde geen afwijkingen. De toename in het relatieve levergewicht is door de commissie als uitgangspunt genomen voor het afleiden van de gezondheidskundige advieswaarde.

**Advies aan de staatssecretaris**

Voor de beroepsmatige blootstelling aan gehydrogeneerd terfenyl komt de commissie tot een gezondheidskundige advieswaarde van 7,4 milligram (mg) per kubieke meter ($m^3$) lucht, als een gemiddelde concentratie over een achturige werkdag.

# executive summary

At request of the Minister of Social Affairs and Employment, the Health Council recommends health based occupational exposure limits (HBR-OEL). This report contains an evaluation of the health hazard and recommendation for hydrogenated terphenyl. The evaluation is performed by the Dutch Expert Committee on Occupational Safety (DECOS), a permanent Committee of the Health Council. Additional information on the task of the Committee can be found at www.healthcouncil.nl. The members of the Committee are listed on the last page of the present advisory report.

**Identified uses**

Hydrogenated terphenyl mixtures are used as a heat transfer fluid (e.g., as a nuclear reactor-coolant), as textile dye carriers, and as plasticizers. The production rate in the European Union is in excess of 1,000 tonnes per annum.

Hydrogenated terphenyls are substances which are very persistent in the environment.

**Health effects**

The main effects reported in humans are skin irritation, headaches and sore throats after accidental exposure. Limited human data are available on the association between exposure to hydrogenated terphenyl at different exposure levels and adverse health effects. Repeated exposure studies in animals revealed increase in organ weights (e.g., the liver), and body weight loss after exposure to hydrogenated terphenyl.

**Health-based recommended occupational exposure limit**

For hazardous substances to which people can be occupationally exposed, the Committee determines whether a concentration can be derived at which no adverse health effects are expected. This HBR-OEL is the base at which the State Secretary can set a legally-binding occupational exposure limit. When deriving an HBR-OEL limit, the principle is applied that an adverse health effect increases with an increasing dose.

**Consulted research**

The Committee has evaluated the studies on exposure to hydrogenated terphenyl, and observed adverse health effects that are suitable for deriving an HBR-OEL. The most clear and evident exposure-related adverse health effects of hydrogenated terphenyl were found in an oral and an inhalation animal experiment.
The repeated exposure studies in rats revealed an increase in organ weights, and body weight loss after inhalation and oral exposure to hydrogenated terphenyl. Histopathology showed no abnormalities. Relative liver weight changes were used to derive an HBR-OEL.

**Recommendation to the State Secretary**

For occupational exposure to hydrogenated terphenyl, the Committee recommends a health-based occupational exposure limit for hydrogenated terphenyl of 7.4 mg per $m^3$ air, which represents a mean concentration during an 8-hour working day.

# 01 scope

## 1.1 Background

At request of the minister of Social Affairs and Employment, the Dutch expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of substances that are used in the workplace. The purpose of the evaluations is to recommend health-based occupational exposure limits (HBR-OELs) for the concentration of the substance in the air, provided the database allows the derivation of such a value.
These recommendations serve as a basis in setting legally binding occupational exposure limit values by the minister.

In this advisory report such a recommendation is made for hydrogenated terphenyl. During use in a nuclear reactor, hydrogenated terphenyl becomes irradiated and conversion of the terphenyl to other hydrocarbons and high polymers occurs to some extent.[1-3] Because differences in toxicity have been observed for irradiated and nonirradiated hydrogenated terphenyl, and the composition of irradiated hydrogenated terphenyl depends on the manner of operation of the nuclear reactor, this evaluation is restricted to the toxicity of nonirradiated hydrogenated terphenyl.[1,4-7]

## 1.2 Committee and procedure

The members of the Committee, and the consulted experts, are listed on the last page this advisory report.

In 2019, the president of the Health Council released a draft of the report for public review. The comments received have been taken into account by the committee in deciding on the final recommendation of the advisory report. The comments, and the replies by the Committee, can be found on the website of the Health Council.

## 1.3 Data

The Committee's recommendation is based on scientific data, which are publicly available. The literature was retrieved from the online databases PubMed, Toxnet and Chemical Abstracts, using a search with the terms "terphenyl hydrogenated" and "CAS 61788-32-7". Additional relevant literature was identified using the references of the retrieved literature and using the online data base from the European Chemicals Agency, regarding REACH legislation. The final search was carried out in November 2019.

## 1.4 Quality assessment

To assess the quality of animal experiments and in vitro studies, the Committee used the criteria set by Klimisch et al. 1997.[8] The following categories of reliability were adopted: 1. Reliable without restriction; 2. Reliable with restrictions; 3. Not reliable, and; 4. Not assignable (Annex A). Studies which were assigned to reliability category 4 (not assignable), Industrial Bio-Test (IBT) studies (considered to be unreliable

unless otherwise stated), and unspecified studies (according to the European Chemicals Agency) were not included in the evaluation.

To assess the quality of human studies, the Committee used the criteria set by Money et al. 2013.[9] The categories of reliability correspond to the data quality categories established by Klimisch et al. (1997): 1. Reliable without restriction; 2. Reliable with restrictions; 3. Not reliable, and; 4. Not assignable (Annex B). In general, the Committee considers studies classified into categories 1 or 2 to be of sufficient quality for the identification of health effects and for the derivation of health-based advisory values. Studies classified into categories 3 or 4 are considered to be of insufficient quality to serve as evidence for deriving HBR-OELs.

# 02 identity, properties and monitoring

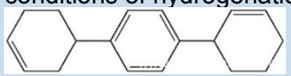
## 2.1 Identity

Hydrogenated terphenyl is a complex mixture of various isomers of ortho-, meta-, and para-terphenyls in various stages of hydrogenation. Five such stages exist for each of the three isomers.[2] Commercial available mixtures (Therminol® 66, HB-40®) are approximately 40% hydrogenated mixtures of all three isomers.[10,11,12] Hydrogenated terphenyl is a substance that is very persistent and very bioaccumulative. It is, therefore, considered by the European Chemicals Agency as a substance of very high concern.[13]

## 2.2 Physical and chemical properties

Physical and chemical properties of hydrogenated terphenyl are shown in table 1.[14-17]

**Table 1.** Physical and chemical properties of hydrogenated terphenyl

| | |
|---|---|
| CAS number<br>EC/EINECS number<br>REACH Reg. Nr. | 61788-32-7<br>262-967-7<br>01-2119488183-33 |
| Synonyms | Hydrogenated diphenylbenzenes; hydrogenated phenylbiphenyls; hydrogenated triphenyls<br>HB-40/00®; Therminol® 66 |
| Use | Used as a plasticizer, and as a heat-transfer medium. |
| Molecular weight | 241 (average)<br>≥ 236 - ≤ 248 |
| Molecular formula | $(C_6H_7)_3$; $C_{18}Hn$ (18<n<36) |
| Physical state | Clear oily pale yellow liquid with characteristic odour at 20°C and 1,013 hPa |
| Solubility | 61 µg/L at 20 °C in water |
| Structure | A mixture of numerous compounds and isomers depending on the degree and conditions of hydrogenation<br>  |
| Relative density | Relative density of the vapour/air-mixture at 20 °C (air = 1), 1.00 |
| Vapour pressure | 13 Pa at 25 °C; 0.002 - 1.781 Pa at 20 - 50 °C |
| Log P octanol/ water | >6,5 |
| Melting point | -32 °C (inchem), -24 °C (echa) |
| Boiling point/ range | 342 °C (1,013 hPa) |
| Flash point | 170 °C (method: Pensky-Martens closed cup); 184 °C (method: Cleveland open cup) |
| Conversion factor | 9.5 mg/m$^3$ = 1 ppm (20 °C, 101 kPa) |

## 2.3 EU classification and labelling

Hydrogenated terphenyl is not classified as a carcinogen.[18]

## 2.4 Validated analytical methods

*Environmental exposure monitoring*

Validated European or international standards for exposure monitoring of hydrogenated terphenyl are not known. Table 2 shows the analytical methods for the determination of hydrogenated terphenyl in air, which are published in the scientific literature.

**Table 2.** Analytical methods for the determination of hydrogenated terphenyl in air.

| Air Sampling method | Analytical Method (use) | Limit of detection or Measuring range in air | Reference |
|---|---|---|---|
| Collection with 40% alcohol solution | Ultraviolet spectrophotometer (workplace testing) | Limit of detection 0.87 mg/m$^3$ | Chai et al. (2004)[19] |
| Adsorption by activated carbon | Desorption by carbon disulfide, analysis by gas chromatography (workplace testing) | Abstract is not clear about matrix analysed | Yu et al. (2010)[20] |
| Trapping about 10 L of air in an impinger containing iso-octane | Gas chromatography utilizing a flame ionization detector and integration of the sum of all chromatographic peaks (inhalation study) | Range: 0-5,000 mg/m$^3$ | Bechtel (1985)[21] |
| Trapping air in glass fibers containing filter paper followed by extraction with n-hexane | Gas chromatography using a flame ionization detector (inhalation study | Range: 0-500 mg/m$^3$ | Farr (1986)[22] |

*Biological exposure monitoring*

Table 3 presents an analytical method for exposure monitoring in biological matrices.

**Table 3.** Analytical methods.

| Sample matrix | Sample preparation | Analytical method | Measuring range | Reference |
|---|---|---|---|---|
| The lung, liver, kidney, gut (mice) | Washed to remove any coolant not located intracellularly, dissolved in a tissue solubilizer and diluted with a luminophor prior to scintillation counting | Scintillation counting | Validated: unknown Results: 0 – 50,000 Disintegrations Per Minute | Adamson and Furlong (1974)[12] |

# 03 sources

## 3.1 Natural sources

No data available.

## 3.2 Man-made sources

### 3.2.1 Production

Terphenyls are produced commercially as ortho, meta, and para isomers. They are produced as the pure compounds. These terphenyls are blended and partially hydrogenated to form principal components.[10] Commercial available hydrogenated terphenyls (Therminol® 66, HB-40®) are approximately 40% hydrogenated mixtures of ortho-, meta-, and para-terphenyls in various stages of hydrogenation, which are clear, yellow oils.[10,1,12]

The partly hydrogenated terphenyl mixture HB-40® is produced commercially by the catalytic hydrogenation of Santowax® to about 40% of maximum theoretical hydrogen uptake. Santowax® has the approximate composition: 7 wt% ortho-terphenyl, 50 wt% meta-terphenyl, 23 wt% para-terphenyl, and 20 wt% triphenylene plus higher polyphenyls.[1]

### 3.2.2 Use

Hydrogenated terphenyl is used as a heat transfer fluid and as a nuclear reactor-coolant, as textile dye carriers, and as plasticizers. The production rate in the European Community is in excess of 1,000 tonnes per annum.[3]

# 04 exposure

## 4.1 General population

No data available.

## 4.2 Working population

In the immediate vicinity of the reactor within the reactor building, a small concentration (0.1 mg/m$^3$) of hydrogenated terphenyl was measured in the atmosphere.[6]

At Chalk River Nuclear Laboratories (CRNL), organic coolant samples were taken over a five-day cycle in all the areas, which are normally accessible locations for workers. The investigation was done as a continuing program, and provided five-day average concentrations for each working area in turn. From such observations, the concentrations of hydrogenated terphenyl (HB-40®) in air have been found to range between 0.89 mg/m$^3$ (average, no data on minimum-maximum levels) in areas containing organic piping and equipment, and 0.094 mg/m$^3$ (average, no data on minimum-maximum levels) in general working areas close by.[23]

No other data on occupational exposure levels are available.

# 05 kinetics and biomonitoring

## 5.1 Absorption, distribution, metabolism and excretion

Hydrogenated terphenyl is rapidly absorbed through the lungs and gastrointestinal tract.[3] Although a limited number of studies indicate that hydrogenated terphenyl is absorbed via the skin, data on skin absorption rates are missing.[24]

Adamson and Furlong (1974) studied clearance and tissue distribution of hydrogenated terphenyl in various organs of mice after inhalation and ingestion of tritiated hydrogenated terphenyl (HB-40®) by using scintillation counting and autoradiography.[12] Following inhalation, particles deposited in the lung were rapidly cleared. A large single oral dose of tritiated hydrogenated terphenyl was mostly cleared from the gut, the liver and the kidneys within a day, and only a low level of radioactivity (<800 desintegrations per minute) was retained up to one week.

Brewster et al. (1992) studied the disposition of Therminol® 66 in rats after a single oral administration at doses of 0, 100, or 300 mg/kg bw, or after inhalation exposure at a concentration of 0 or 350 mg/m$^3$, once for 6 hours.[11] They determined the effects on the hepatic and renal drug metabolizing enzymes ethoxycoumarin O-deethylase (ECOD), and aryl hydrocarbon hydroxylase (AHH). AHH is also known as CYP1A1. ECOD metabolizes 7-alkoxycoumarin to 7-hydroxycoumarin, and is cytochrome P-450-dependent. Approximately 30% of the oral dose was absorbed from the gastrointestinal tract. There was little accumulation in tissues, and the whole-body half-life was less than 1 day. Induction of drug-metabolizing enzymes was evident only at the highest doses, and the liver was more sensitive to the inducing effects of Therminol® 66 than was the kidney. ECOD was more sensitive to Therminol® 66 than was AHH, and inhalation produced a greater effect than did dietary exposure.[11]

## 5.2 Biomonitoring

No data available.

# 06 effects

## 6.1 Observations in humans

### 6.1.1 Health effects due to single or short-term exposure

Limited data are available on the health effects of hydrogenated terphenyl in humans.

Although there have been accidental releases of hot hydrogenated terphenyl from pressure in the vicinity of experimental equipment, the symptoms reported (headache and sore throat) subsided within 24 hours in every case.[23] Table 4 presents the results of a skin sensitization study performed in humans with hydrogenated terphenyl.[25] No evidence was reported that the test material acted as a sensitizer in any of the individuals included in the test.

**Table 4.** Health effects due to short-term exposure.

| Reference | Substance | Study design and Population | Data on exposure and health assessment | Results | Remarks |
|---|---|---|---|---|---|
| Shelanski and Smith (1979)[25] | Mixture of hydrogenated terphenyls (HB-40®)<br><br>Impurities: 0.15% phenyl cyclohexane, 6.79% high boilers | Human voluntary experiment; skin sensitization study<br><br>51 subjects (M7/F44) per dose | *Method*: Repeated Insult Patch Test<br>*Dose*: 0.2 ml neat test material as supplied<br>*Induction exposure*: 15 induction doses during 5 weeks, 24 hours per dose<br>*Challenge exposure*: 1 challenge dose, exposure 24 hours<br>*Evaluation*: 24, 48 and 72 hours after challenge<br>*Interval between last induction dose and challenge dose*: 14 days | No instances of irritation or sensitization | No guideline followed, well-documented, available as unpublished report, minor restrictions in reporting, but otherwise adequate for assessment<br><br>Reliability: 2 |

### 6.1.2 Health effects due to long-term exposure

Table 5 presents the characteristics of a study on long-term exposure of workers to hydrogenated terphenyl.[23]

**Table 5.** Cohort study on occupational exposure to hydrogenated terphenyl.

| Reference | Study design and population | Data on exposure and health assessment | Results | Remarks |
|---|---|---|---|---|
| Weeks and Lentle (1970)[23] | USA cohort study;<br>n=47 male workers, regularly and frequently exposed, matched with n=47 male workers, casual and infrequently exposed to hydrogenated terphenyl<br><br>*Location*: workers exposed in working areas of a nuclear reactor, and other research facilities<br><br>*Mean age*: 33 years | Hydrogenated terphenyl, not specified.<br><br>Average exposure levels measured in the working environment: $9.4x10^{-5}$ - $8.9x10^{-4}$ mg/l (corresponds with 0.094 - 0.89 mg/m$^3$)<br><br>Regularly and frequently exposed workers: consistent exposure (40 h/week, 5 days/week); reference group, casual and infrequent exposure<br><br>Effect parameters: brief medical history on known renal and pulmonary disease, history on skin disease; at t=0 and after one year: clinical and biochemical analysis (blood pressure, pulmonary function, urinary and blood sampling) | No differences between regularly/frequently exposed workers, and reference group<br><br>Creatinin clearance in regularly/frequently exposed workers was decreased after one year. However, a follow-up study showed no differences between regularly/frequently exposed workers and reference group after six years.[26] | Limitations include: no data on exposure monitoring methods; no details on the substance the workers are exposed to (radiated and/or irradiated hydrogenated terphenyl); limited information on smoking habits (group of casual and infrequently exposed workers contained more and heavier smokers than regularly and frequently exposed workers); limited number of cases<br><br>Additional information:<br>In cases of accidental exposure, symptoms reported were headache and sore throat, which subsided within 24 hours<br><br>Reliability: 3 |

Overall, the Committee notes that there is a limited number of reliable data on exposure of humans.

### 6.1.3 Carcinogenicity

No data available.

### 6.1.4 Reproductive and developmental effects

No data available.

## 6.2 Animal experiments

Studies performed in laboratory animals are summarized in Annex C.

### 6.2.1 Health effects due to single exposure

The summarized studies in Annex C (Table C1) comprise one inhalation study in rats, and five oral studies of which four were performed in rats and one in mice. Furthermore, three rabbit studies using dermal applications, and one rabbit study with ocular exposure were available.

In an acute inhalation study performed by Bechtel (1985), six groups of 12 rats per group were exposed to hydrogenated terphenyl once for 4 hours.[21] Mean exposure concentrations ranged from 2.5 to 4.7 g/m$^3$. Immediately after exposure, observations included: salivation, wet fur on the ventral side (due to salivation), discharges and/or encrustations about the nose and eyes, laboured breathing, procumbent posture, and fur coated with test material. No terminal necropsy findings were reported, which are considered to be related to the test material.[21]

The acute oral toxicity of hydrogenated terphenyl is low, showing rat and mouse oral LD50 values in excess of 10 g/kg bw.[5,27,28] After oral exposure to a single dose of hydrogenated terphenyl of 10 g/kg bw, observations on rats included hypoactivity, diarrhea, faeces-stained and urine-stained fur. No abnormalities were noted at gross necropsy.[28]

In a dermal irritation study according to the method of Draize, the researchers reported that hydrogenated terphenyl was found to be mild or not irritating to rabbit skin. The primary dermal irritation index (PDII) was 2.0 on a scale of 8.0 (0.0 (no irritation) up to 8.0 (extreme irritation).[27] In another study, dermal exposure of rabbits to hydrogenated terphenyl resulted in a PDII of 0.1 (minimal irritation) on a scale of 8.0. Effects were fully reversible.[29] A study for acute dermal toxicity in rabbits showed that no deaths resulted from a dermal (occlusive) dosage of 2 g/kg bw.[30] There were no abnormal clinical and behavioural observations, and no abnormalities were seen at gross necropsy.

In an eye irritation study in rabbits, the Draize score was 0.3 (no irritation) on a scale of 110 (very severe irritation) after a single exposure to 0.1 ml undiluted hydrogenated terphenyl.[31]

Based on the observed health effects due to single exposure in animals, the Committee concludes that the acute toxicity of hydrogenated terphenyl in animals is low after oral, inhalation and dermal exposure. In addition,

hydrogenated terphenyl is considered to be not irritating to rabbit skin or eyes.

### 6.2.2 Health effects due to short-term exposure

Three animal studies on short-term exposure to hydrogenated terphenyl were identified. Two studies were rated with a high reliability score, and are briefly described below. More details on the three studies are given in Annex C, Table C2.

An oral dose range finding study was performed in rats, which were exposed to dose levels of 0, 1,000, 5,000, 10,000, or 20,000 ppm (corresponding with concentrations of 0, 60, 300, 600, or 1,200 mg/kg bw/day) for two weeks.[32] After two weeks of exposure mean body weights were reduced in the males and females at the 10,000 ppm (reduction of 10% and 8%, respectively), and 20,000 ppm dose levels (reduction of 27% and 17% respectively). The female rats at 5,000 ppm also exhibited an 8% reduction in mean body weight. Mean kidney weights were reduced in males and females at the 20,000 ppm dose level (approximately 22% and 20%, respectively). Dose-related increases were observed in the mean absolute liver weights, and relative liver to body weights of the treated males and females. Increases noted in mean liver weights ranged from 10% in the low-dose females to 144% in the high-dose females. Similar increases were observed in the treated males. Liver gross changes were seen in animals at dose level 5,000, 10,000, and 20,000 ppm. In this study, the no-observed-adverse-effect-level (NOAEL) was 1,000 ppm in the diet, corresponding with 60 mg/kg bw/day.[32]

A dermal repeated dose administration study was performed in rats.[24] Hydrogenated terphenyl was admininistrated by dermal application to 5 males and 5 females per dose and control (abraded skin and unabraded skin), at dose levels of 0, 125, 500 and 2,000 mg/kg bw, 5 days per week for 3 consequitive weeks. At macroscopic examination, commonly observed findings were thickening and crust formation of the skin, which were observed at all applied doses in both sexes. Gross and microscopic changes on the skin application sites were observed at the dosage levels of 125, 500 and 2,000 mg/kg bw/day. There were no other clinical effects observed. The authors considered the findings to be related to the dermal application of hydrogenated terphenyl. The distribution and severity of the skin changes were generally more pronounced among male and female rabbits at the 2,000 mg/kg bw.[33]

Overall, the Committee notes that there is a limited number of reliable animal data on the association between exposure to hydrogenated terphenyl at different dose levels and adverse effects after short-term exposure of animals. The available data show that limited changes were seen after exposure to hydrogenated terphenyl. The Committee considers the increase in (relative) liver weights in animals to be related to the systemic effects of hydrogenated terphenyl.

### 6.2.3 Health effects due to subchronic exposure

Annex C (Table C3) gives an overview of four animal expirements on subchronic exposure to hydrogenated terphenyl and health effects. Two studies with a high reliability score are described below.

In a thirteen week inhalation toxicity study performed by Farr et al. (1986, 1989), 15 rats per sex per group were exposed to hydrogenated terphenyl at concentrations of 0 (group I), 10 (group II), 100 (group III) and 500 mg/m$^3$ (group IV) for 6 hours per day, 5 days per week.[10,22]

Predominant clinical signs included lacrimation and rough coat in treated males, and dried brown material about the face in treated females. Liver weight changes were observed in animals at different exposure levels. The mean absolute and relative liver weights were increased for all groups of treated males compared to control males. The differences between treated and control males were statistically significant for all comparisons, except for the absolute liver weights of group II and III males (10 and 100 mg/m$^3$, respectively). Mean absolute and relative liver weights were not statistically significant changed in the exposed females compared to control females. There were no other exposure-related findings in the organ weight data of the males or females. There were no effects on gross pathological findings, and no effects on non-neoplastic histopathological findings. No hematological changes were noted by the researchers. The mean serum glutamic oxaloacetic transaminase and glucose levels were decreased for the group IV females (500 mg/m$^3$) compared to the control females, and the mean total protein, albumin and calcium levels were increased for group III and IV females (100 and 500 mg/m$^3$, respectively) compared to control females. However, the researchers concluded that the majority of values were within historical control ranges, and were considered toxicologically not significant. The mean blood urea nitrogen level was increased for group IV males at test week 14 compared to control males. However, values were within historical ranges and no renal pathology was seen. Therefore, the researchers considered this difference not to be toxicologically significant.[10,22] The NOAEL was reported to be 100 mg/m$^3$.

In an oral study performed by Farr *et al.* (1984, 1989), groups of 12 male and 12 female rats were given diets containing 0, 50, 200 or 2,000 ppm hydrogenated terphenyl for 14 weeks.[10,34] Combined male and female nominal dietary doses of hydrogenated terphenyl was 0, 3, 12 and 120 mg/kg bw/day, respectively.

At the highest dose, body weight loss and increases in liver, kidney and adrenal weights were observed, but no other effects. There was an increased incidence of renal tubular lesions (foci of tubular epithelial cell hypertrophy, and basophilia, a non-neoplastic histopathological finding) in high dosed males when compared to control males. The researchers considered the finding to represent regeneration. Effects were observed

on haematological findings (decrease in haemoglobin concentration, haematocrit and erythrocyte counts, slight increase in mean platelet count, statistically significant in high dosed males), and clinical biochemistry (mean cholesterol increased in high dosed males, mean glucose decreased in high dose dfemales, and mean calcium levels increased in mid- and high dosed females). The NOAEL identified by the researchers was 12 mg/kg bw/day (200 ppm).

Overall, the Committee notes that there is a limited number of reliable animal data on subchronic exposure to hydrogenated terphenyl. The Committee concludes that hydrogenated terphenyl may cause an increase in (relative) organ weights in animals (*i.e.*, the liver, the kidneys and the adrenal glands), which is considered to be related to the systemic adverse health effects of hydrogenated terphenyl.

### 6.2.4 Non-carcinogenic adverse health effects due to long-term exposure

No data available.

### 6.2.5 Carcinogenicity

Data on the potential carcinogenicity of hydrogenated terphenyl is very limited. No carcinogenicity data are available after inhalation or oral exposure.

Annex C (Table C4) presents dermal carcinogenicity studies on hydrogenated terphenyl, performed by Henderson and Weeks (1973).[7] The results of these studies indicate that the possibility of cancer occurring in the skin of mice exposed to hydrogenated terphenyl is negligible. However, the Committee is of the opinion that dermal carcinogenicity studies were too limited for a conclusion.

### 6.2.6 Genotoxicity

Three in vitro studies were identified, presenting the results of bacterial and mammalian cell mutation assays.[27,35,36] The studies showed that hydrogenated terphenyl is not genotoxic in vitro. More details are given in Annex C, Table C5.

The mutagenic potential of hydrogenated terphenyl was also determined by a rat bone marrow cytogenetics assay.[37] Rats were exposed to hydrogenated terphenyl at doses of 0, 250, 1,250 and 2,500 mg/kg bw. Cells from exposed animals and controls, were evaluated microscopically for mitotic index, and chromosomal abnormalities. No chromosomal damage was noted. Details are presented in Annex C, Table C6.

The Committee notes that the bacterial and mammalian cell mutation assays, and the in vivo chromosome aberration assay were negative. Therefore, the Committee concludes that there are no indications of genotoxicity.

### 6.2.7 Reproductive and developmental effects

*Fertility*

An oral two-generation reproductive toxicity study in male and female rats was performed with hydrogenated terphenyl. Details are given in Annex C, Table C7.[38] There were no adverse reproductive effects in any of the measured parameters/indices in adult rats or their offspring. On the basis of these findings, the Committee noted that no reproductive effects were seen in rats at the highest intake levels of 1,000 ppm (62.0 mg/kg bw/day for males and 81.2 mg/kg bw/day for females).

*Development*

Two developmental toxicity studies with hydrogenated terphenyl in animals were identified and are summarized below.[39,40] Details are shown in Annex C, Table C8.

Developmental toxicity was tested by oral administration of hydrogenated terphenyl in rats from day 6 to 15 of gestation at 125, 500 and 1,500 mg/kg bw/day.[40] Maternal toxicity was observed from 500 mg/kg bw/day, leading to foetotoxicity and malformations at 1,500 mg/kg bw/day. The NOAEL for maternal toxicity was 125 mg/kg bw/day, the NOAEL for foetotoxicity was 500 mg/kg bw/day.

An oral dose range finding study was performed in a teratology study with hydrogenated terphenyl in rats from days 6 to15 of pregnancy.[39] The maternal NOAEL was 250 mg/kg bw/day. The developmental NOAEL was 1,000 mg/kg bw/day.[39]

The Committee noted that developmental toxicity could be related to maternal toxicity, because in both studies maternal toxicity is observed at lower exposure levels than developmental toxicity. Therefore, the Committee is not able to conclude whether hydrogenated terphenyl could induce direct adverse effects on the developing embryo.

*Lactation*

No data available.

## 6.3 Summary

A number of studies are available on the potential toxicity of hydrogenated terphenyl. The majority of these studies are animal experiments or in vitro assays.

*Observations in humans*

Data on humans are limited to one skin sensitization study, and one study on long-term exposure of workers in a nuclear reactor. The results of the skin sensitation study were negative. The study on long-term exposure is of limited quality, one of the reasons being inadequate quantification of the

exposure levels to which the participants were exposed. After accidental exposure, the main adverse health effects reported by workers were skin irritation, headaches and sore throats. Therefore, the Committee is of the opinion that human studies on the toxicity of hydrogenated terphenyl were too limited to allow derivation of a HBR-OEL.

*Animal experiments*

A number of animal acute toxicity studies have been performed that report LD50 values, ranging from more than 10 to 25 g/kg bw (oral administration, rats). The Committee concludes that the acute toxicity of hydrogenated terphenyl in animals is low after oral, inhalation and dermal exposure. In addition, hydrogenated terphenyl is considered to be not irritating to rabbit skin or eyes.

The Committee noted that there is a limited number of reliable animal data on short-term exposure. Increase in (relative) liver weights in animals after oral intake of hydrogenated terphenyl (15 days, 7 days/week), is considered to be related to the systemic effects of hydrogenated terphenyl.

Based on the results of animal studies on subchronic exposure to hydrogenated terphenyl, the Committee concludes that, although histopathology showed no abnormalities, body weight loss and increase in (relative) organ weights (e.g., the liver) are the most relevant observed effects after inhalation or oral intake of hydrogenated terphenyl up to 14 weeks.

*Carcinogenicity and genotoxicity*

The results of the animal studies on dermal carcinogenicity indicate that skin cancer risk in mice, exposed to hydrogenated terphenyl, is negligible. No other animal carcinogenicity experiments have been performed. The Committee notes that the bacterial and mammalian cell mutation assays and an in vivo chromosome aberration assay in rats were negative. The Committee concludes that there are no indications of genotoxicity.

*Reproductive and developmental effects*

The Committee concluded that there is insufficient data available to classify hydrogenated terphenyl as a reproductive toxicant.
The Committee noted that developmental toxicity could be related to maternal toxicity, because in both animal studies maternal toxicity is observed at lower exposure levels than developmental toxicity. Therefore, the Committee is not able to conclude whether hydrogenated terphenyl could induce direct adverse effects on the developing embryo.
The Committee noted that there is no data available on the effects of hydrogenated terphenyl on or via lactation.

# 07 existing guidelines, standards and evaluation

## 7.1 General population

Guidelines or standards for exposure limits for hydrogenated terphenyl for the general population are not known.

## 7.2 Working population

Principal effects of exposure to hydrogenated terphenyl listed bij OSHA are: HE3 (Chronic (Cumulative) Toxicity-Long-term organ toxicity other than nervous, respiratory, hematologic or reproductive) and HE10 (Respiratory Effects Other Than Irritation-Cumulative lung damage).[41]
The European Chemicals Agency agreed that terphenyl hydrogenated meets the criteria set out in Article 57 of REACH for identification as substance of very high concern, and included terphenyl hydrogenated in the Candidate List for eventual inclusion in Annex XIV.[14,42]

### 7.2.1 Occupational Exposure Limits

Occupational exposure limits for hydrogenated terphenyl in some European countries and the USA, are presented in Table 6.

**Table 6.** Occupational exposure limits (as 8-hour time-weighted averages and 15 minutes time weighted averages) for hydrogenated terphenyl in various countries.

| Country - organisation | TWA, 8 hours | TWA, 15 minutes | Reference |
|---|---|---|---|
| The Netherlands (2019) (adopted from European Union) | 19 mg/m$^3$ | 48 mg/m$^3$ | 43 |
| European Union (2017) | 19 mg/m$^3$ | 48 mg/m$^3$ | 44 |
| - SCOEL (1994) | 2 ppm (19 mg/m$^3$) | 5 ppm (48 mg/m$^3$) | 3 |
| Germany | | | |
| - AGS (2017) | 19 mg/m$^3$ (inhalable fraction) | | 45 |
| Norway (2009) | 0.4 ppm; 4.4 mg/m$^3$ | - | 46 |
| Denmark (2011) | 0.4 ppm; 4.4 mg/m$^3$ | - | 47 |
| USA | | | |
| - ACGIH (2001) | 0.5 ppm; 5 mg/m$^3$ | | 2 |
| - OSHA PEL | 0.5 ppm; 5 mg/m$^3$ | | 41 |
| - NIOSH | 0.5 ppm; 5 mg/m$^3$ | | 41 |

ACGIH, American Conference of Governmental Industrial Hygienists; AGS, Ausschuss für Gefahrstoffe; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Admninistration; PEL, Permissable Exposure Limit; SCOEL, Scienific Committee on Occupational Exposure Limits; TWA, time weighed average contration.

In the evaluation by the SCOEL (1994) the quantitative hazard assessment is based on animal data as it is concluded that there are no available human data relating to exposure levels in excess of 0.1 ppm (0.95 mg/m$^3$).[3] Based on the inhalation study of Farr et al. (1989), the SCOEL used a NOAEL of 10 ppm (95 mg/m$^3$) as a starting point.
To allow for the extrapolation from animals to humans, an uncertainty factor of 5 was considered appropriate. The recommended 8-hour time weighted average (TWA) by the SCOEL is 2 ppm (19 mg/m$^3$).
Because of the reports of irritation in workers exposed to unspecified

concentrations of hydrogenated terphenyl, a STEL (15 minutes) of 5 ppm (48 mg/m$^3$) was proposed by the SCOEL to limit peaks in exposure, which could result in irritation.

### 7.2.2 Classification on the carcinogenic properties

So far known, hydrogenated terphenyl is not classified as a carcinogen.

### 7.2.3 Classification on the reproduction toxic properties

So far known, hydrogenated terphenyl is not classified as toxic to reproduction and development.

### 7.2.4 Biological limit values

No biological limit values have been set.

### 7.2.5 Skin and sensitization notation

In various countries, a skin notation was considered not to be necessary.[3,43,44]

# 08 hazard assessment

## 8.1 Hazard Identification

The main adverse health effects observed in humans were skin irritation, headaches, and sore throats after accidental exposure. These effects were reported, presumably following accidental spillages, and exposure to unspecified concentrations of hydrogenated terphenyl. The Committee notes that there is a limited number of reliable data on exposure to humans.

Animal experiments on health effects due to single exposure indicate that the acute toxicity of hydrogenated terphenyl in animals is low after oral, inhalation, and dermal exposure. In addition, hydrogenated terphenyl is considered to be not irritating to rabbit skin or eyes. Repeated dose studies in animals revealed body weight loss, and increase in (relative) organ weights after inhalation or oral exposure to hydrogenated terphenyl. Because body weight loss was observed not only in the oral study, but also in highly exposed male rats in an inhalation study, the Committee considers body weight loss to be an adverse health effect, which is not related to palatability problems. In addition, taking also into account the effects on liver weight, the Committee is of the opinion that the increase in relative liver weight is an adverse health effect, although histopathological findings are negative. While the absolute liver weight was statistically significantly increased only at the high exposure level in male rats from the inhalation study, relative liver weights were statistically significantly increased at all exposure levels. Overall, the Committee considers relative liver weight changes the most relevant observed adverse health effect for hydrogenated terphenyl-induced toxicity.

## 8.2 Quantitative hazard assessment

### 8.2.1 Critical study

In deriving an HBR-OEL, the committee prefers using data from epidemiological studies rather than animal experiments, because epidemiological data do not involve the uncertainties associated with the biological differences between animals and humans. Furthermore, the exposure conditions in epidemiological studies reflect real life exposure circumstances in an occupational setting. Data from animal experiments are considered only if epidemiological data are of insufficient quality or too limited. In the case of hydrogenated terphenyl epidemiological data are limited and insufficient, and, therefore, the committee used data from animal experiments.

The most clear and evident exposure-related effects of hydrogenated terphenyl on organ weights are found in an inhalation and oral study in rats, which was prublished by Farr et al. (1989).[10] Increased absolute liver weights, and liver/body weight ratios, were seen at the high-exposure level in both sexes from the oral study, and in high-exposed males from the inhalation study. Absolute kidney weights and kidney/body weight ratios were increased only in the high-dose animals of both sexes in the oral study. Haematology and clinical chemistry showed no abnormalities;

changes observed were within the historical control ranges. Gross and histopathological examinations revealed no lesions to hydrogenated terphenyl administration in either study. Although the significance of organ weight changes in absence of pathological observations is uncertain, the committee is of the opinion that exposure to hydrogenated terphenyl is harmful to the liver and the kidneys, which is supported by observations in other studies.[5,12]

Inhalation studies are most relevant for the occupational situation, but the Committee also considers systemic health effects observed in oral studies, which it considers relevant when these effects are also expected to occur after inhalation exposure. Therefore, the Committee has retrieved and examined the results of the inhalation study, as well as the oral study published by Farr et al. (1989).[10,22,34] Because no significant increase in the liver weight, and the liver to body weight ratio, were noted in female rats from the inhalation study, the Committee decided to use the data from male rats only. This means that the Committee considers male rats to be more vulnerable to hydrogenated terphenyl than female rats.

### 8.2.2 Derivation and recommendation of an HBR-OEL (8-hour TWA)

In deriving an HBR-OEL, the Committee performed a benchmark dose-analysis (BMD-analysis). Details on the analyses are shown in Annex D. The lowest BMDL is used as a starting point in deriving an HBR-OEL.The BMDL is the 95% lower confidence limit of the BMD that corresponds with a defined critical effect size (CES). Literature shows that there is no consensus on critical effect sizes of organ weights.[48] Small increase in liver weight without significant histological findings, or marked changes in clinical chemistry, is interpreted as an adaptive and not as an adverse health effect. In addition, it is important to consider that the liver weight may vary in healthy animals to up to 20%.[49] The Committee notes that in the inhalation study and in the oral study by Farr et al. (1989), increase in liver to body weight ratio was more than 20% at the highest exposure level. Also, a decrease of body weight gain was evident at high exposure in male rats in the inhalation study. The Committee is of the opinion that a CES of 20% is appropriate for changes in liver to body weight ratios in rats.[49]

For the establishment of an HBR-OEL several aspects have to be considered:

1. *Interspecies differences*. The Committee noted that in this case the effects were systemic, and, therefore a default uncertainty factor of three should be applied.
2. *Intraspecies differences*. Due to possible differences among workers, the Committee is of the opinion that another uncertainty factor of three is required.[50]
3. *Differences beween experimental conditions and exposure pattern of the worker*. Data were derived from an animal experiment, in which rats were exposed to hydrogenated terphenyl for a period of approximately

14 weeks. The Committee is of the opinion that an adjustment factor of 2 is required to extrapolate from subchronic to chronic exposure for which an HBR-OEL is derived.[51,52]

The Committee estimated the following HBR-OELs (8-hour TWA, Table 7):

**Table 7** Health-based recommended occupational exposure limit (8-hour TWA).

| Exposure in rats | Critical effect size | BMDL | Uncertainty factors | HBR-OEL |
|---|---|---|---|---|
| Inhalation ($mg/m^3$) | Relative liver weight 0.20 | 134 $mg/m^3$ | 3 (interspecies)<br>3 (intraspecies)<br>2 (subchr-chronic) | 7.4 $mg/m^3$ |
| Oral (mg/kg/day) | Relative liver weight 0.20 | 19.1 mg/kg/day (corresponds with 133.7 $mg/m^3$, based on 100% absorption, 70 kg body weight, and a respiratory volume of 10 $m^3$/working day)# | 3 (interspecies)<br>3 (intraspecies)<br>2 (subchr-chronic) | 7.4 $mg/m^3$ |

# The Committee used default values for absorption, body weight and respiratory volume, because true values are unknown.

Overall, the Committee recommends a health-based occupational exposure limit for hydrogenated terphenyl of 7.4 $mg/m^3$, as an 8-hour TWA.

### 8.2.3 Short term exposure limit (STEL; 15-minutes TWA)

Based on the available literature indicating that the acute toxicity of hydrogenated terphenyls is low, the Committee concludes that a STEL is not applicable.

### 8.2.4 Ceiling value

Not applicable.

## 8.3 Classification

### 8.3.1 Classification as a carcinogenic substance

No human or animal carcinogenicity data are available on inhalation or oral exposure. The results of the study on dermal carcinogenitity in mice indicate that the possibility of cancer occurring in the skin exposed to hydrogenated terphenyl is negligible. Overall, the Committee concludes that data are too limited to classify hydrogenated terphenyl as a carcinogen.

### 8.3.2 Classification as reproduction toxic substance

No studies in humans are available. In two well-performed animal studies, maternal toxicity occured before adverse health effects on development were noted. Since maternal toxicity by itself may induce developmental effects, it is unclear to the DECOS whether hydrogenated terphenyl is able to induce developmental effects. No data are available on effects on lactation. Overall, the DECOS is of the opinion that, because of maternal

toxicity, there are insufficient data for classifying hydrogenated terphenyl as a reproduction toxic substance.

## 8.4 Skin notation

The purpose of a skin notation is to indicate the need to prevent skin contamination when systemic effects may result from percutaneous absorption of a substance as a gas, a solid, or a liquid. To determine whether a skin notation needs to be applied, the Committee uses the document “Strategy for assigning a skin notation” by the European Centre for Ecotoxicology and Toxicology of Chemicals (Strategy for assigning a “skin notation”, ECETOC Document No. 31 (Revised 1993). According to the guidance, a skin notation is warranted when human experience indicates the importance of skin penetration. A skin notation should be applied when exposure of 2,000 $cm^2$ of skin (both hands and forearms) to hydrogenated terphenyl during one hour could result in an absorbed amount exceeding 10% of the amount that can be absorbed via the lungs on exposure for eight hours to the HBR-OEL. Although a limited number of studies indicate that hydrogenated terphenyl is absorbed via the skin, data on skin absorption rates are missing. Therefore, the DECOS is not able to conclude whether a skin notation is recommendable.

## 8.5 Groups at extra risk

No data available.

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# annexes

# A criteria for testing reliability of animal and in vitro studies

To assess the reliability of animal and in vitro studies, the Committee uses the criteria set by Klimisch et al. 1997.[8] A summary of the criteria of the reliability scores is given below. Only studies with a reliability score of 1 or 2 are considered in assessing genotoxicity and carcinogenicity.

*Reliability 1 (reliable without restriction)*
For example, guideline study (OECD, etc.); comparable to guideline study; test procedure according to national standards (DIN, etc.).

*Reliability 2 (reliable with restrictions)*
For example, acceptable, well-documented publication/study report which meets basic scientific principles; basic data given: comparable to guidelines/standards; comparable to guideline study with acceptable restrictions.

*Reliability 3 (not reliable)*
For example, method not validated; documentation insufficient for assessment; does not meet important criteria of today standard methods; relevant methodological deficiencies; unsuitable test system.

*Reliability 4 (not assignable)*
For example, only short abstract available; only secondary literature (review, tables, books, etc.).

# B reliability testing of epidemiological studies

To assess the reliability of epidemiological studies, the Committee uses the criteria set by Money et al.(2013).[9] A summary of the reliability categories set by Money et al. (2013) is given below. Only studies with a reliability score of 1 or 2 are considered in assessing genotoxicity and carcinogenicity.

**Reliability 1 (reliable without restriction)**

*Chronic, non-specific outcomes*

Appropriate study design to research question.

1. Selected subjects or persons at risk represent appropriate exposure distributions. Adequate procedures of follow-up and reduction of loss to follow up were performed.
2. Exposure assessment was made independent of outcome with validated methods, preferentially with individual exposure data.
3. Effect data were collected independently from exposure status, using standardized data collection procedures/registries.
4. The possibility of serious bias has been reduced by design, controlled through statistical adjustment, and/or quantified through sensitivity analyses.
5. The sample/exposure range was sufficient to study the question under investigation, so that effects estimates are not constrained by high imprecision.
6. The data were analysed using appropriate statistical techniques to address the research questions and model assumptions.
7. The methodology and results were comprehensively and transparently reported according to relevant guidelines (e.g., the STROBE guidelines for observational data, Von Elm et al. 2007).

*Acute or specific outcomes*

The same principles should be applied as for chronic, non-specific outcomes. The focus lies more with how well exposure has been characterised, and the disease outcome is defined.

**Reliability 2 (reliable with restrictions)**

*Chronic, non-specific outcomes*

Applies to studies which possess most of the qualities of studies with reliability 1. The overall quality is comprised due to minor, but obvious, methodological limitations. Examples include well-designed and conducted studies, but with limited measurement data, possibility of some residual confounding, some imprecision due to small sample size or low exposure range.

*Acute or specific outcomes*

The same principles should be applied as for chronic, non-specific outcomes. Examples of shortcomings may include a lack of individual exposure data, and effects derived from self-reported outcomes.

Note: some studies with serious methodological limitations may provide reliable information for an acute or specific outcome.

**Reliability 3 (not reliable)**

The studies fail to meet one or more of the most basic standards necessary to interpret epidemiologic research, such as appropriate study design to the research question. Shortcomings may include using census job titles as a surrogate for exposure.

**Reliability 4 (not assignable)**

This includes studies or data which do not give sufficient details about methodology used, or which are short listed in abstracts or secondary literature.

# C effects observed in animal studies

**Table C1.** Health effects due to single exposure

Inhalation exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Bechtel (1985)[21] | Mixture of hydrogenated terphenyls (Therminol® 66) | Acute toxicity test<br><br>Sprague-Dawley rats,<br>Males and females;<br>N=6/sex/group | Concentrations: 0, 2.5, 3.6, 4.4, and 4.7 g/m$^3$ (aerosol)<br><br>Single exposure: 4 hours<br>Observation period: 14 days, animals held in ambient and elevated temperatures<br><br>Endpoint: LC50 | LC50 > 4.7 g/m$^3$<br><br>Clinical signs immediately after exposure: salivation, wet fur on the ventral side, discharge and/or encrustation about the nose and eyes; labored breathing; prostrate condition (not specified) and fur coated with test material | Test Guideline equivalent or similar to OECD Guideline 403 (Acute Inhalation Toxicity); GLP-compliant study; unpublished report; no restrictions, adequate for assessment; reliability 1 |

## Oral exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Clark et al (1979)[27] | Therminol® 66.<br><br>General composition: modified terphenyls, no details | Acute toxicity test<br><br>Female Fischer 344 Rats; N=5/ group;<br>control animals not mentioned | Dosages spaced at about 0.1 log increments. Maximum dose applied: 24 g/kg bw (by gavage)<br><br>Test period: 14 days<br><br>Endpoint: LD50 | LD50 > 24 g/kg bw<br><br>No clinical signs of toxicity other than diarrhea during the first 24 hours (dose not specified) | GLP compliance not specified; reliability 1 |
| Branch (1980)[28] | Mixture of hydrogenated terphenyls (HB-40®)<br><br>Impurities: 0.15% phenyl cyclohexane, 6.79% high boilers | Acute toxicity test<br><br>Male and female Sprague-Dawley rats; N=5/sex/ group, no control animals | Single dose by gavage, 10 g/kg bw<br><br>Observation period: 15 days<br><br>Endpoint: LD50 | LD50 > 10 g/kg bw<br><br>Observations (n observed/dosed):<br>- hypoactivity (10/10)<br>- diarrhea (8/10)<br>- feces-stained fur (10/10)<br>- urine-stained fur (10/10) | Test Guideline equivalent or similar to the deleted OECD Guideline 401 (Acute Oral Toxicity); Guideline 401 was deleted in 2002; GLP compliance; reliability 1 |
| Adamson and Weeks (1973)[5] | hydrogenated terphenyl (HB-40®) or mineral oil | Acute Toxicity test. Hooded male rats; N=6/group | Various doses by gavage, between 1 and 50 g/kg bw.<br><br>Endpoint: LD50 | LD50 approximately 17.5 g/kg bw | GLP compliance not specified; no data on clinical observations and gross pathology; reliability 2 |
| Adamson and Weeks (1973)[5] | hydrogenated terphenyl (HB-40®) or mineral oil | Acute Toxicity test<br><br>Male mouse JAX® Black Mice (strain not specified); N=6/group | Exposure: various doses by gavage, between 1 and 50 g/kg bw<br><br>Endpoint: LD50 | LD50 approximately 12.5 g/kg bw | GPL compliance not specified; no data on clinical observations and gross pathology; reliability 2 |
| Hasegawa et al. 1989[53] | Hydrogenated terphenyl | Acute toxicity test.<br><br>Male and female Wistar rats; N=10/ group | 6 increasing dose levels, not specified<br><br>Observation period: 14 days<br><br>Endpoints: clinical signs, changes in tissue, organ toxicity, and LD50 | Acute toxic symptom: sedation<br><br>Changes in tissue: congestion of viscera<br><br>LD50 male: 25 g/kg bw.<br>LD50 female: 24 g/kg bw | Documentation insufficient for assessment; reliability 3 |

## Dermal exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Chow and Besserman (1980)[30] | Mixture of hydrogenated terphenyls (HB-40®)<br><br>Impurities: 0.15 phenyl cyclohexane, 6.79% high boilers | Acute dermal toxicity test<br><br>Male and female New Zealand White rabbits; N=5/sex | Occlusive, shaved dorsal surface<br><br>Dose: 2 g/kg bw<br><br>Exposure: 24 hours continuous<br>Observation period: 14 days | No exposure-related effects | Test Guideline equivalent or similar to OECD Guideline 402 (Acute Dermal Toxicity); reliability 1 |
| Branch et al. (1980)[29,33] | Mixture of hydrogenated terphenyls (HB-40®)<br><br>Impurities: 0.15 phenyl cyclohexane, 6.79% high boilers | Irritation/corrosion study<br><br>Male and female New Zealand White rabbits; N=3/sex | Draize test: occlusive, dorsal surface, intact and abraded skin<br><br>Amount applied: 0.5 mL neat substance to each application site<br><br>Exposure: 24 hours<br>Observation period: 14 days<br><br>Reading times primary dermal irritation index (PDII): 24, 72 hrs | Primary dermal irritation index (PDII): 0.1 on a scale of 8.0 (fully reversible); erythema score 0.1 on a scale of 4 (fully reversible); edema score: 0 on a scale of 4 (fully reversible) | Reliability 1 |
| Clark et al. (1979)[27] | Therminol® 66<br><br>General composition: modified terphenyls, no details | Irritation/corrosion study<br><br>Male and female New Zealand White rabbits; N=3/sex | Draize test: skin abraded and unabraded<br><br>Reading times: 24 and 72 hours after application | Primary dermal irritation index (PDII): 2 on a scale of 8.0. Impossible to calculate mean erythema score and mean edema score from data | Reliability 2 |

Ocular exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Chow (1980)[31,33] | Mixture of hydrogenated terphenyls (HB-40®)<br><br>Impurities: 0.15 phenyl cyclohexane, 6.79% high boilers | Eye irritation study<br><br>Male and female New Zealand White rabbits; N=3/sex | Draize test: ocular contact, right eye<br><br>Dose: 0.1 mL of undiluted Terphenyl hydrogenated<br><br>Reading times Draize score: 24, 48 and 72 hours | Conjunctivae score: 0 on a scale of 3; Chemosis score: 0 on a scale of 4; Cornea opacity score: 0.06 on a scale of 4 (fully reversible within 48h);<br>Iris score: 0 on a scale of 2; Draize score: 0.3 on a scale of 110 (fully reversibel within 48h) | Reliability: 2 |

## Table C2. Health effects due to short-term exposure

Inhalation exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Adamson et al (1969)[54] | Compressed air containing a mixture of ortho-, para-, and meta-terphenyls, with a small concentration of higher polymers | Mouse strain not specified; sex not specified; N=16/ group | Exposure: 0.5 g/m$^3$ (aerosol), 7 hours/day for 2, 4, 6 or 8 days or 4 hours/day for 2 or 4 days<br><br>Endpoints: animal weight, food consumption, hematocrit levels and hematologic counts, alveolar cell counts, abnormalities in paraffin sections from the lung, liver, kidney, bladder, adrenal, spleen, heart, brain, and bone marrow | Weight loss after exposure during 7 hours/day compared to controls. After exposure during 4hours/day weight gain was similar compared to controls<br><br>Histopathology of the lungs showed change of mitochondria in alveolar type 2 cells, however this change was reversible 42 days after final exposure | Documentation infsufficient for assessment: no statistical analysis, no data on exact exposure concentration, no data on percentage of higher polymers in oil; reliability 3 |

## Oral exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Farr (1985)[32] | Mixture of hydrogenated terphenyls. (Therminol® 66®) Assume 100% active ingredient | Male and female Sprague-Dawley rats; N=5/sex/group | Dose (by feed): 0 (c, control) 1,000; 5,000; 10,000; 20,000 ppm, corresponding with 60; 300; 600; 1,200 mg/kg bw/day<br><br>Exposure: 15 days, 7 days/week<br><br>Endpoints: physical observations, body weight, food consumption, gross postmortem examinations; no histopathological examinations | NOAEL: 60 mg/kg bw/day<br>LOAEL: 300 mg/kg bw/day.<br><br>Data in mean%±SD, increasing dose<br><br>Males<br>Kidneys to terminal bw ratio:<br>0.85±0.03 (c), 0.86±0.05, 0.88±0.08, 0.91±0.03, 0.93±0.05<br>Liver to terminal bw ratio:<br>3.33±0.18 (c), 3.88±0.21, 6.68±0.15, 8.71±0.45, 10.15±0.26<br><br>Females<br>Kidneys to terminal bw ratio:<br>0.86±0.08 (c), 0.93±0.09, 0.89±0.09, 0.87±0.03, 0.85±0.04<br>Liver to terminal bw ratio:<br>3.13±0.16 (c), 3.66±0.15, 5.03±0.39, 6.80±0.51, 9.55±0.81<br><br>Food consumption increased at 10,000 ppm and 20,000 ppm (males only)<br><br>Liver gross pathological changes: enlargement, surface irregularities (raised tan foci) and discolorations (primarily mottled tan) at 5,000, 10,000 and/or 20,000 ppm | GLP-compliant study; statistical evaluations were not done because of small numbers of animals on test in this range-finding study; reliability 1 |

## Dermal exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Johnson (1981)[24] | High Boiling Liquid, Hydrocarbon (HB-40®) | Male and female New Zealand White Rabbits; N=5/sex/ group | Dermal: occlusive, abraded skin and unabraded skin<br><br>Dose (nominal): 0, 125, 500, and 2,000 mg/kg bw/day<br><br>Exposure: 6 hours/day, 5 days/week for 21 days<br><br>Endpoints: mortality, clinical effects, body weights, dermal irritation, clinical chemistry, organ weights, macroscopy and microscopy of selected tissues | Dermal irritation (very slight to moderate erythema, edema, atonia, skin pealing, coriaceous and very slight to marked skin fissures were observed for some rabbits in all test groups)<br><br>Macroscopy: thickening and crust formation at 125, 500 and 2,000 mg/kg bw among male and females.<br>Microscopy: acanthosis, hyperkeratosis, inflammatory cell infiltrates. Microabscesses at 2,000 mg/kg bw. The distribution and relative severity of the skin changes were generally more pronounced among male and female rabbits at the 2,000 mg/kg bw dosage level | GLP compliant, well-documented study; reliability 1 |

**Table C3.** Health effects due to subchronic exposure

Inhalation exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Farr (1986)[22]<br>Farr et al. (1989)[10] | Mixture (Therminol® 66) | Male and female Sprague-Dawley rats; N= 15/sex/ group | Concentration (aerosol):<br>- Group I: 0 mg/m³ air (control);<br>- Group II: 10 mg/m³ air corresponding to 11.4 mg/m³ (males) and 11.3 mg/m³ (females);<br>- Group III: 100 mg/m³ air corresponding to 98.7 mg/m³ (males) and 98.4 mg/m³ (females);<br>- Group IV: 500 mg/m³ air corresponding to 480 mg/m³ (males) and 479 mg/m³ (females)<br><br>Exposure: 6 hours/day, 5 days/week for 13 weeks<br><br>Endpoints: clinical signs, body weights, major organ weights haematology and clinical chemistry, gross postmortem examination, histopathology. | NOAEL was 100 mg/m³<br><br>Clinical effects observed (increased incidences of excess lacrimation and rough coat exhibited by all groups of treated males compared to control males; dried brown material about the face exhibited by females, primarily in the mid- and high-dose animals)<br><br>Effects on body weight and weight changes:<br>- terminal mean body weight males, mean (g)±SD: 586±33, 570±41, 594±54, 543±15*<br><br>Effects on organ weights<br>- absolute liver weight males, mean (g)±SD: 18.62±1.42, 19.76±2.29, 20.74±2.77, 21.60±3.40*<br>- liver/total body weight males (x100) mean (g)±SD: 3.15±0.16, 3.46±0.25**, 3.49±0.24**, 3.97±0.37**<br><br>Statistically significant: *p≤0.05, **p≤0.01<br><br>Mortality observed (N=1 in group I female); no other exposure-related effects observed | OECD Guideline 413 (subchronic inhalation toxicity: 90-Day Study), GLP compliant; reliability 1 |

## Oral exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Farr et al (1989)[10]<br>Nair (1984)[34] | Therminol® 66 | Male and female Sprague-Dawley (CD) rats; N=12/ sex/group | Dose: 0 (c; control), 50, 200, or 2,000 ppm (corresponding to 0, 3, 12 and 120 mg/kg bw/day)<br><br>Exposure for approximately 14 weeks<br><br>Endpoints: observations for clinical signs, body weights,ophthalmoscopy, haematology and clinical chemistry, major organ weights, gross and histopathology | NOAEL 12 mg/kg bw/day (200 ppm)<br><br>Data, mean±SD, increasing dose<br><br>Males<br>Terminal body weight (g):<br>476±49 (c), 503±41, 486±57, 464±54<br>Liver weight (g) mean±SD:<br>13,17±1.46 (c), 13.82±1.42, 14.35±2.38, 19.32±2.49**<br>Liver to body weight ratio (g/100g):<br>2.77±0.09 (c), 2.75±0.15, 2.94±0.21, 4.18±0.42**<br>Kidney weight (g):<br>3.13±0.40 (c), 3.23±0.35, 3.15±0.32, 3.36±0.38<br>Kidney to body weight ratio (g/kg):<br>6.61±0.81 (c), 6.42±0.58, 6.52±0.58, 7.27±0.59*<br>Adrenal to body weight ratio (mg/g):<br>1.13±0.21 (c), 1.07±0.22, 1.11±0.17, 1.18±0.18<br><br>Females<br>Terminal body weight (g):<br>280±26 (c), 280±36, 287±30, 262±17<br>Liver weight (g):<br>7.52±1.5 (c), 7.52±1.05, 7.82±0.84, 9.07±1.16**<br>Liver to body weight ratio (g/100g):<br>2.68±0.25 (c), 2.69±0.21, 2.69±0.18, 3.45±0.29**<br>Kidney weight (g):<br>1.81±0.16 (c), 1.91±0.28, 1.98±0.27, 2.02±0.23<br>Kidney to body weight ratio (g/kg):<br>6.63±0.58 (c), 6.84±0.60, 6.90±0.93, 7.70±0.52*<br>Adrenal to body weight ratio (mg/g):<br>2.34±0.31 (c), 2.43±0.40, 2.28±0.43, 2.73±0.34*<br><br>Statistically significant, *p≤0.05, **p≤0.01 | Reliability 1 |

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| | | | | Effects on haematological findings (decrease in haemoglobin concentration, haematocrit and erythrocyte counts, slight increase in mean platelet count, statistically significant in high-dose males) and clinical biochemistry (mean cholesterol increased in high dose males, mean glucose decreased in high dose females, mean calcium levels increased in mid- and high dose females) | |
| Adamson and Weeks (1973)[5] | hydrogenated terphenyl (HB-40®) or mineral oil | Male JAX® mouse (strain not specified); N=10/ group | Dose (by gavage): 20, 250, 600, 1,200, 2,000 mg/kg bw/day<br><br>Exposure: 112 days; 1 or 2 doses/week.<br><br>Endpoints:histopathology and total protein in liver (µg/mg tissue) | NOAEL was 600 mg/kg body weight/day<br><br>Mitochondrial changes in epithelial cells of proximal tubulus. At high doses these cells became necrotic as interstitial nephritis and scarring developed. The nephritis was irreversible and followed 16 weeks of 1,200 mg/kg bw/day. Hepatic changes were observed only at the ultrastructural level where abundant smooth endoplasmic was seen | Documentation infsufficient for assessment; reliability 3 |

## Percutaneous exposure

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Verkkala and Havolainen (1983)[55] | A terphenyl mixture, 40% aromatic bonds hydrogenated | Male Wistar rats; number of animals (test and controls) unknown | Percutaneous, tail, 1.5 cm distal to the anus, 12 $cm^2$<br><br>Absorbed dose: 0.23±0.05 g/12 $cm^2$ skin in 3h; cumulative total dose: 39 g/kg bw/8 weeks; exposure: 3 hours/day, 4-8 weeks.<br><br>Endpoint: Motor conduction time/muscle responses | No systemic toxicity (The total absorbed terphenyl dose exceeded the acute LD50 reported by the producer as 10 g/kg body wt). Dark discolorisation of the skin without appearance of papillomas.<br>No effect on motor conduction time (no demyelination), polyphasia and progressively decreasing muscle responses (signs of axonal damage) | Reliability 3 |

## Table C4. Carcinogenicity studies in animals

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Henderson and Weeks 1973[7] | hydrogenated terphenyl (HB-40®), Landsteiner tar (positive control) | Skin exposure study<br><br>Male and female Balb/c Mouse; N=10/sex | Dermal, dose: 50 mg HB-40® or 270 mg tar (control) applied at regular intervals (weekly)<br>Exposure: 37 weeks with terphenyl, hydrogenated and then 22 weeks with croton oil (solvent)<br><br>Endpoints:all skin tumours, skin cancers, mammary tumours, long tumours, leukemia, pancreatic adeno cancers, ovarian tumours | After 37 weeks, no skin tumour had appeared on skin painted with terphenyl, hydrogenated; proportion of autopsied positive controls with skin cancer: 20/23<br><br>Proportion of autopsied mice with skin cancer after 59 weeks: HB-40®: 0/24 | Reliability 2 |
| Henderson and Weeks 1973[7] | hydrogenated terphenyl (HB-40®), Landsteiner tar (positive control) | Skin exposure study<br><br>Male and female Balb/c mouse; N=10/sex | Dermal dose: 50 mg/week<br><br>Exposure: 14 weeks with terphenyl, hydrogenated (5, 4, 3, 2 or 1 times/week), therafter 13 weeks, twice weekly with croton oil)<br><br>Endpoint: skin carcinogenicity | No skin tumours observed | Reliability 2 |
| Henderson and Weeks 1973[7] | hydrogenated terphenyl (HB-40®), Landsteiner tar (positive control) | Skin exposure study<br><br>Male/female PLA mouse; N=10/sex | Dermal dose: 50 mg/week<br><br>Exposure: 37 weeks, once/week.<br><br>Endpoint: skin carcinogenicity | No skin carcinogenicity, the tumours found fell within normal histological range | Reliability 2 |

**Table C5.** Bacterial and mammalian cell mutation assays

| Reference | Substance | Cell system | Data on exposure | Results | Remarks |
|---|---|---|---|---|---|
| Clark et al. (1979)[27] | Therminol® 66<br><br>General composition: modified terphenyls, no details | Bacterial reverse mutation assay: *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100; with and without metabolic activation | Test concentrations: up to 10,000 µg/plate | Mutagenicity: no effect (no details)<br><br>Cytotoxicity not observed up to 10,000 µg/plate | Reliability 1 |
| Kulik (1978)[36] | 40% hydrogenated terphenyls | Bacterial reverse mutation assay: *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100; with and without metabolic activation | Test concentrations: 0.01, 0.04, 0.2, 1.0, 3.0, 10.0 µL/plate<br><br>3 positive controls (with or without S-9 mix), 3 replications. | Mutagenicity: no effect<br><br>No cytotoxicity but tested up to limit concentrations | Comparable to guideline study; reliability 2 |
| Godek et al. (1985)[35] | Mixture Therminol® 66 | Mammalian cell gene mutation assay; Chinese hamster ovary (CHO), cell line CHO-K1-BH4; with and without metabolic activation | Test concentrations: 0, 25, 50, 75, 100 and 300 µg/mL<br><br>Test included positive control | Mutagenicity: no effect<br><br>Cytotoxicity not bserved up to 1,000 µg/mL (precipitation of the test article was apparent at all doses above 100 µg/mL) | GLP compliant, unpublished report, adequate assessment; reliability 1 |

**Table C6.** Rat bone marrow clastogenicity

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Blazak (1986)[37] | Complex mixture Therminol® 66 | Mammalian Bone Marrow Chromosome Aberration Test<br><br>Male/female Fischer 344 Rat; N=18/sex/ dose/ sampling time | Single intraperitoneal injection of 0, 250, 1,250, and 2,500 mg/kg bw<br><br>Sampling time 6, 12, 24 hours after dosing<br><br>Negative control: corn oil<br>Positive controle: 0.2 mg/kg bw triethyenemelamine (TEM)<br><br>Endpoints: microscopically evaluation for mitotic index (percent metaphase cells) and chromosomal abnormalities | Genotoxicity: no effect<br><br>Results 24h (negative control, 2,500 mg/kg bw and positive control respectively):<br><br>Mitotic Index (mean % ± SEM):<br>F: 5.05±0.44, 6.36±1.07, 3.31±0.34<br>M: 5.82±0.31, 7.22±0.98, 4.79±0.65.<br><br>Number of aberrant cells: total number of cells with aberrant chromosomes including aneuploidy and polypoloidy (mean % ± SEM)<br>F: 0, 0.83±0.83, 28.33±5.75<br>M: 0.33±0.33, 0.33±0.33, 24.33±3.71<br><br>Overall frequency of aberrations (mean % ± SEM):<br>F: 0, 0.01, 1.10±0.27<br>M: 0.003±0.003, 0.003±0.003, 0.86±0.11.<br><br>Toxicity: no effects | OECD Guideline 475; reliability 1 |

**Table C7.** Reproductive oral toxicity study in animals

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Naylor and Ruecker (1991)[38] | Complex mixture of terphenyl and quaterphenyl isomers (Therminol® 66) | Two-Generation Reproduction Toxicity Study<br><br>Male and female Sprague-Dawley rats; N=30 adults/ sex/group | Exposure route: oral by feed<br><br>F0 Adults: 0, 30, 100, 300 and 1,000 ppm (1.8, 6.1, 18.5 and 62.0 mg/kg bw/day for males, and 2.5, 8.3,24.4 and 81.2 mg/kg bw/day for females); 7 days/week<br><br>F1a Adults: 0, 30, 100, 300 and 1,000 ppm (1.9, 6.1, 18.2 and 63.1 mg/kg bw/day for males, and 2.4, 8.1,24.3 and 80.6 mg/kg bw/day for females); 7 days/week<br><br>Endpoints: Two-generation reproductive toxicity, body weights, food consumption, survival, clinical observations, gross and microscopic examinations | PO (First parental animals): effects on body weight or weight gain (during the last three weeks in 1,000 ppm dietary level males of the F0 generation and in 1,000 ppm dietary level F1a dams during gestation), effects on food consumption and compound intake (decrease in part of the females and increase in part of the males), other effects not specified or negative<br><br>F1 generation: no effect | OECD Guideline 416, GLP compliant; unpublished report, no restrictions, adequate for assessment; reliability 1 |

**Table C8.** Developmental oral toxicity study in animals

| Reference | Substance | Study design and animal species | Data on exposure and effect endpoints | Results | Remarks |
|---|---|---|---|---|---|
| Nair (1985)[39] | Purity: 100% (assumed for preparation of dosing solutions) (Therminol® 66) | Female Sprague-Dawly rats; N=5/ group | Exposure route: oral by gavage<br><br>Exposure: 0 (control), 125, 250, 500, 1,000 and 2,000 mg/kg bw/day; days 6-15 of gestation<br><br>Endpoints:<br>Females: weight, physical evaluation, food consumption, post mortem evaluation (day 20 of gestation), recording of uterine implantation data<br>Fetuses: weight, sex, external malformation | Embryotoxic/ teratogenic effects:<br>- At 500 mg/kg bw/day: a slight decrease in mean maternal food consumption,<br>- At 1,000 mg/kg bw/day: indication of maternal toxicity (reduction in mean weight gain and reduction in food consumption<br>- At 2,000 mg/kg bw/day: maternal toxicity (reduced weight gain and food consumption), embryotoxic/fetotoxic effects (increase in resorption data, decrease in mean fetal weight) | Reliability 1 |
| Farr (1986)[40] | Mixture, concentration Presumed to be 100% for purposes of formulating dosing solutions (Therminol® 66) | Prenatal Developmental Toxicity Study<br><br>Female Sprague-Dawly rats; N=24/ group | Exposure route: oral by gavage<br><br>Exposure: 0 (control), 125, 500 and 1,500 mg/kg bw/day; gestation days: from day 6-15 of pregnancy; once per day.<br><br>Endpoints:<br>Females: body weights, food consumption, physical evaluation, gross postmortem evaluation, corpora lutea/uterine implantation data registration<br>Fetus: weight, sex, gross examination/ malformations, visceral evaluation/ microdissection procedure or evaluation for skeletal malformations/ ossification variations | - At 500 mg/kg bw/day: slight maternal toxicity (reduced food consumption)<br>- At 1,500 mg/kg bw/day: severe maternal toxicity (mortality 12.5%, reduced mean weight data and reduced weight gain during the treatment period, reduced food consumption, and physical findings) as well as fetotoxicity (reduced fetal weights, increased incidence of fetuses with certain ossification variations); however, no clear embryotoxicity, a statistically significant increase in the incidence of fetuses with skeletal malformations (cleft palate, rostral area of nose elevated) with a unique syndrome of observations (related to the severe maternal toxicity?) | According to OECD Guideline 414; reliability 1 |

# D benchmark dose analysis

**Data**

The most clear and evident dose related effects of hydrogenated terphenyl are found in a inhalation and oral study in rats published by Farr et al (1989).[10,22,34] Tables D1 and D2 show data on the liver and liver to body weight ratio changes, from which a BMDL could be calculated.

**Table D1.** Effects of hydrogenated terphenyl in rats following inhalation exposure for 13 weeks[10,22]

Male rats

| Exposure level | 0 mg/m³ | 10 mg/m³ | 100 mg/m³ | 500 mg/m³ | Number of animals |
|---|---|---|---|---|---|
| Terminal body weight (g), mean±SD | 586±33 | 570±41 | 594±54 | 543±53* | n=14;15;14;15 respectively |
| Liver weight (g), mean±SD | 18.62±1.42 | 19.76±2.29 | 20.74±2.77 | 21.60±3.40* | n=15, all groups |
| Liver to body weight ratio (g/100g), mean ±SD | 3.15±0.16 | 3.46±0.25** | 3.49±0.24** | 3.97±0.37** | n=14;15;14;15 respectively |

Female rats

| Exposure level | 0 mg/m³ | 10 mg/m³ | 100 mg/m³ | 500 mg/m³ | Number of animals |
|---|---|---|---|---|---|
| Terminal body weight (g), mean±SD | 299±25 | 305±19 | 308±33 | 298±26 | n=14;12;15;14 respectively |
| Liver weight (g), mean±SD | 10.77±1.30 | 10.41±1.02 | 10.35±1.20 | 11.04±1.34 | n=14;12;15;14 respectively. |
| Liver to body weight ratio (g/100g), mean ±SD | 3.61±.034 | 3.41±0.23 | 3.37±0.35 | 3.72±0.33 | n=14;12;15;14 respectively |

*/** Statistically significant at p≤0.005* or p≤0.01**.

**Table D2.** Effects of hydrogenated terphenyl in rats following oral exposure for 13 weeks[10,34]

Male rats

| Target exposure level, (ppm) | 0 | 50 | 200 | 2,000 |
|---|---|---|---|---|
| Target exposure level, (mg/kg/day) | 0 | 3 | 12 | 120 |
| Estimated dietary test article consumption (mg/kg/day) | 0 | 3.90±0.25 | 15.9±0.91 | 156±10.08 |
| Terminal body weight (g), mean±SD | 476±49 | 503±41 | 486±57 | 464±54 |
| Liver weight (g), mean±SD | 13.17±1.46 | 13.82±1.42 | 14.34±2.34 | 19.32±2.49** |
| Liver to body weight ratio (g/100g), mean±SD | 2.77±0.09 | 2.75±0.15 | 2.94±0.21 | 4.18±0.42** |

Female rats

| Target exposure level, (ppm) | 0 | 50 | 200 | 2,000 |
|---|---|---|---|---|
| Target exposure level, (mg/kg/day) | 0 | 3 | 12 | 120 |
| Estimated dietary test article consumption (mg/kg/day) | 0 | 3.90±0.25 | 15.9±0.91 | 156±10.08 |
| Terminal body weight (g) mean±SD | 280±26 | 280±36 | 287±30 | 262±17 |
| Liver weight (g), mean±SD | 7.52±1.5 | 7.52±1.05 | 7.82±0.84 | 9.07±1.16** |
| Liver to body weight ratio (g/100g), mean±SD | 2.68±0.25 | 2.69±0.21 | 2.69±0.18 | 3.45±0.29** |

** Statistically significant at p≤0.01. N=12 animals per group, except female rats exposed to 200 ppm (n=11 for terminal body weight and liver to body weight ratio).

**BMD-analysis**

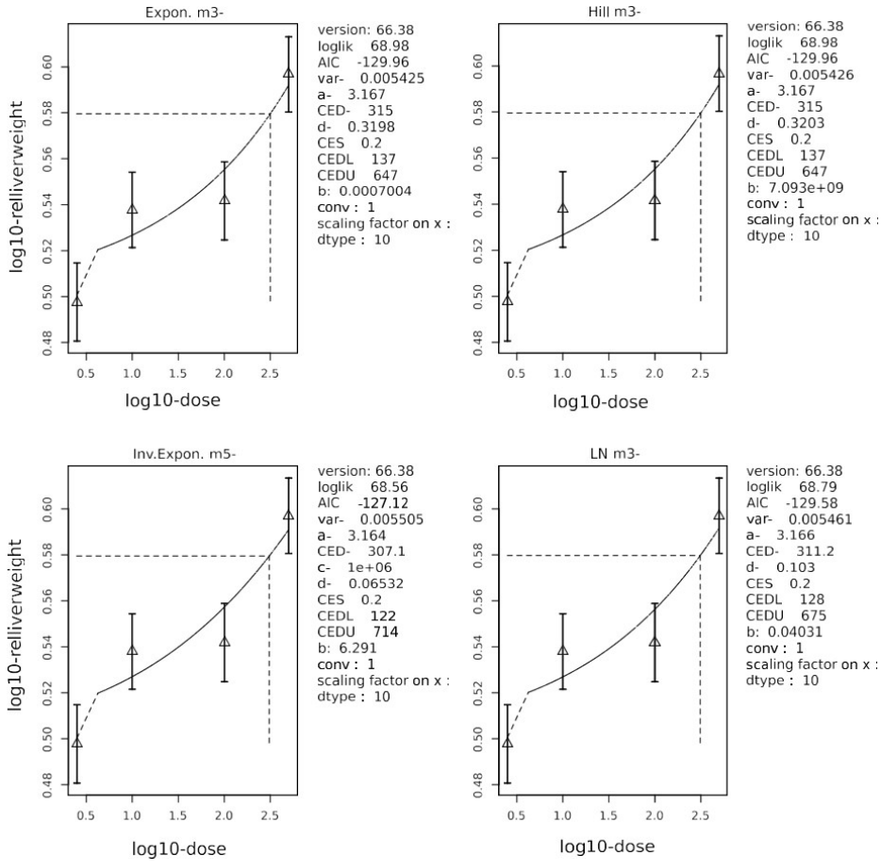
The Committee used the BMD-modelling method and software provided by the European Food Safety Authority (EFSA) and the National Institute for Public Health and the Environment (RIVM, Netherlands).[56] Results of the BMD-analyses are presented in Table D3.

**Table D3.** Benchmark Dose modelling.

| Exposure | Sex | Weights for Model Averaging | Value for critical effect size (CES) | BMD confidence intervals | Final BMD Values (BMDL-BMDU) |
|---|---|---|---|---|---|
| Inhalation ($mg/m^3$) | Males | 0.3259 EXP<br>0.3259 HILL<br>0.0788 INVEXP<br>0.2695 LOGN | relative liver weight<br>CES 0.20 | 0.9 | 134 - 590 |
| Oral (mg/kg/day) | Males | 0.2274 EXP<br>0.2274 HILL<br>0.2862 INVEXP<br>0.259 LOGN | relative liver weight<br>CES 0.20 | 0.9 | 19.1 – 72.4 |

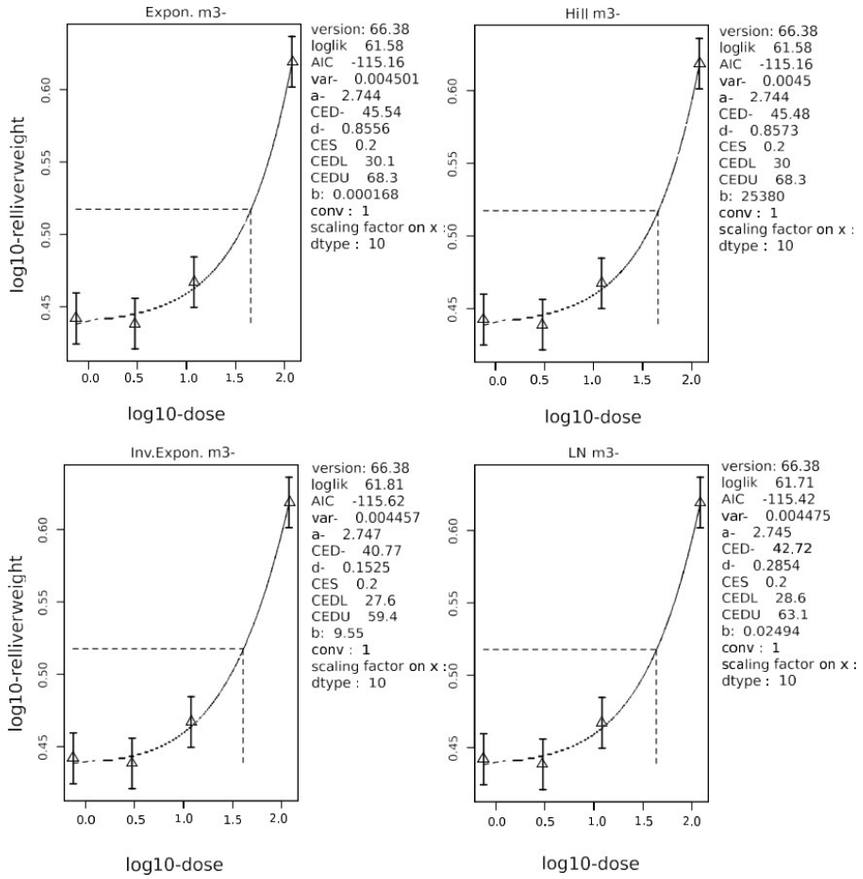
## Fitted Models Inhalation data

| model | converged | loglik | npar | AIC |
|---|---|---|---|---|
| full model | yes | 71.47 | 5 | -132.94 |
| null model | yes | 46.92 | 2 | -89.84 |
| Expon. m3- | yes | 68.98 | 4 | -129.96 |
| Expon. m5- | no | 68.98 | 5 | -127.96 |
| Hill m3- | yes | 68.98 | 4 | -129.96 |
| Hill m5- | yes | 65.84 | 5 | -121.68 |
| Inv.Expon. m3- | yes | 63.67 | 4 | -119.34 |
| Inv.Expon. m5- | yes | 68.56 | 5 | -127.12 |
| LN m3- | yes | 68.79 | 4 | -129.58 |
| LN m5- | yes | 65.83 | 5 | -121.66 |




## Fitted Models Oral data

| model | converged | loglik | npar | AIC |
|---|---|---|---|---|
| full model | yes | 62.17 | 5 | -114.34 |
| null model | yes | 13.31 | 2 | -22.62 |
| Expon. m3- | yes | 61.58 | 4 | -115.16 |
| Expon. m5- | yes | 62.12 | 5 | -114.24 |
| Hill m3- | ®yes | 61.58 | 4 | -115.16 |
| Hill m5- | ®yes | 62.12 | 5 | -114.24 |
| Inv.Expon. m3- | ®yes | 61.81 | 4 | -115.62 |
| Inv.Expon. m5- | ®yes | 62.12 | 5 | -114.24 |
| LN m3- | ®yes | 61.71 | 4 | -115.42 |
| LN m5- | ®yes | 62.12 | 5 | -114.24 |



## The Committee

**The members of the Dutch Expert Committee on Occupational Safety for the toxicologic evaluation and recommendation of a health-based occupational exposure limit for hydrogenated terphenyl**

- F.G.M. Russel, Professor of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, *chairman*
- P.J. Boogaard, Professor of Environmental Health and Human Biomonitoring, Wageningen University and Research Centre, and Toxicologist, Shell International BV, The Hague (until December 31, 2019)
- H. Bouwmeester, associate professor of toxicology, Wageningen University and Research Centre, Wageningen (from January 1, 2020)
- R. Houba, Occupational Hygienist, Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
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- E.D. Kroese, Toxicologist, TNO, Zeist
- C.F. Kuper, Toxicologic pathologist, Utrecht
- H. van Loveren, Emeritus Professor of Immunotoxicology, Maastricht University
- I.M.C.M. Rietjens, Professor of Toxicology, Wageningen University and Research Centre (until December 31, 2019)
- M. Rooseboom, toxicologist, Shell International BV, The Hague (from January 1, 2020)
- G.B.G.J. van Rooy, Occupational physician/toxicologist, Arbo Unie Expert Centre for Chemical Risk Management, and Radboud UMC Outpatient Clinic for Occupational Clinical Toxicology, Nijmegen
- L.A. Smit, Epidemiologist, Institute for Risk Assessment Sciences, University Utrecht
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**Consulted experts**

- A.H. Piersma, Professor of Reproductive and Developmental Toxicology, Utrecht University, and National Institute for Public Health and the Environment, Bilthoven, *structurally consulted expert* (until December 31, 2019)

**Observers**

- H. Stigter, Occupational Physician, Inspectorate SZW, Ministry of Social Affairs and Employment, The Hague
- D. Theodori, Social and Economic Council, The Hague

**Scientific secretary**

- B.E. Smink, Health Council of the Netherlands, The Hague

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