The MAK Collection for Occupational Health and Safety

Di(2-propylheptyl) phthalate

MAK Value Documentation – Translation of the German version from 2015

A. Hartwig[1,*], MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Geb. 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

***** *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords: di(2-propylheptyl) phthalate; respiratory tract; peroxisome proliferation; liver; carcinogenicity; MAK value; maximum workplace concentration

Citation Note: Hartwig A, MAK Commission. Di(2-propylheptyl) phthalate. MAK Value Documentation – Translation of the German version from 2015. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2017 Apr;2(2):337-356]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2026. https://doi.org/10.34865/mb5330654e5817_w

Republished (online): 07 Aug 2026

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb5330654e5817

Manuscript completed: 16 Dec 2013

Published (online): 29 Apr 2017

The commission established rules and measures to avoid conflicts of interest.

This work is licensed under a Creative Commons Attribution 4.0 International License.

Di(2-propylheptyl) phthalate / Bis(2-propylheptyl) benzene-1,2-dicarboxylate

MAK Value Documentation

A. Hartwig[1,*], MAK Commission[2,*]

DOI: 10.1002/3527600418.mb5330654e5817

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated di(2-propylheptyl) phthalate [53306-54-0] considering all toxicological endpoints. Available publications and unpublished study reports are described in detail. Critical effect is the peroxisome proliferating activity in the liver which has also been observed with other phthalates. Di(2-propylheptyl) phthalate is less potent as a peroxisome proliferator than the structurally very similar di(2-ethylhexyl) phthalate, which is a rat liver carcinogen. No carcinogenicity study has been performed on di(2-propylheptyl) phthalate but due to the similarity to di(2-ethylhexyl) phthalate, liver carcinogenicity cannot be excluded. Therefore, di(2-propylheptyl) phthalate is classified in Category 3B for suspected carcinogens. Di(2-propylheptyl) phthalate is not genotoxic in vitro; in vivo data are missing. Only a 5-day inhalation study has been performed. Possible long-term effects on larynx, trachea or goblet cell hyperplasia which are target organs of di(2-propylheptyl) phthalate and of other phthalates cannot be evaluated based on this study. No maximum concentration at the workplace (MAK value) can be derived. Di(2-propylheptyl) phthalate shows no developmental toxicity in rats up to an oral dose of 1000 mg/kg body weight and day which is toxic to the dams. Skin contact is not expected to contribute significantly to systemic toxicity. Limited data show no sensitization.

Keywords

di(2-propylheptyl) phthalate; phthalic acid bis (2-propylheptyl)ester; bis(2-propylheptyl) phthalate; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

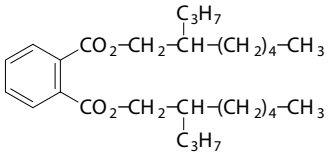
Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute for Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Geb. 50.41, 76131 Karlsruhe, Germany

[2] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

[*] Email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

Di(2-propylheptyl) phthalate

MAK value	**–**
Peak limitation	**–**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity (2014)	**Category 3B**
Prenatal toxicity	**–**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	phthalic acid bis (2-propylheptyl)ester
Chemical name (CAS)	Bis(2-propylheptyl) phthalate
CAS number	53306-54-0
Structural formula	
Molecular formula	$C_{28}H_{46}O_4$
Molecular weight	446.67
Melting point	– 8°C (BASF AG 2000 a)
Boiling point at 7 hPa	251 – 253°C (BASF AG 1995 e)
Density at 20°C	0.9624 g/cm³ (BASF AG 1995 a)
Vapour pressure at 20°C	$3.7 \cdot 10^{-8}$hPa (BASF AG 1999)
log K_{OW}[1)] at 25°C	> 6.0 (BASF AG 1995 a)
Solubility at 25°C	< 0.1 µg/l water (BASF AG 1995 a)
1 ml/m³ (ppm) ≙ 18.53 mg/m³	**1 mg/m³ ≙ 0.054ml/m³ (ppm)**

1) octanol/water partition coefficient

Di(2-propylheptyl) phthalate is used as a plasticizer in PVC, polyurethane and epoxide resin adhesives, contact adhesives, printing inks, anti-corrosion paints, antifouling paints and as a component in lubricants. It is produced via the dimerization of *n*-valeraldehyde and hydration to 90% 2-propylheptanol with 10% 2-propyl-4-methylhexanol and subsequent esterization with phthalic acid anhydride. In this process, > 99.5% of the phthalic acid ester with C10 alcohol is produced (BASF SE 2014).

Di(2-propylheptyl) phthalate is a phthalic acid dialkylester with a branched C10 alcohol chain. This consists of the main isomer 2-propylheptanol and a process-related byproduct, 2-propyl-4-methylhexanol. The type of branch is therefore closely defined, and no other isomers occur. Thus, di(2-propylheptyl) phthalate consists of 81% di(2-propylheptyl) phthalate, 18% asymmetric 2-propylheptyl-2′-propyl-4-methylhexyl phthalate and 1% di(2-propyl-4-methylhexyl) phthalate. Because of this narrow, closely defined isomer spectrum, di(2-propylheptyl) phthalate differs from diisodecyl phthalate (DIDP), which consists of more complex isomer mixtures of C9 to C11 alcohols. Inversely, as a result of the process, no di(2-propylheptyl) phthalate is contained in the isomer mixture of diisodecyl phthalate (BASF SE 2014).

As a di(2-propylheptyl) phthalate isomer mixture is always formed during production, the percentage of di(2-propylheptyl) phthalate itself is given in the studies if this has been reported.

1 Toxic Effects and Mode of Action

Toxicologically, di(2-propylheptyl) phthalate behaves in a way similar to that of diisodecyl phthalate (documentation "Diisodecyl phthalate, mixture of isomers" 2011). The substance differs considerably, however, from di(2-ethylhexyl) phthalate (DEHP) and di-*n*-butyl phthalate (DBP) with regard to various end points (see documentation "Di(2-ethylhexyl)phthalate (DEHP)" 2009; documentation "Di-n-butyl phthalate" 2013). For example, di(2-propylheptyl) phthalate does not cause testicular toxicity, endocrine effects or prenatal toxicity.

After inhalation exposure of rats to aerosol concentrations of 1000 mg/m^3 for 5 days, increases in liver and lung weights, macrophage overloading, foam cell infiltrates and epithelial hyperplasia in the terminal bronchi, a lymphoreticular reaction in the mediastinal lymph nodes and hyperplasia in the trachea were observed. At 250 mg/m^3, the effects in the respiratory tract were much less pronounced. At concentrations of 50 mg/m^3 and above, the incidence of goblet cells in certain areas of the nasal conchae was increased in all animals more or less regardless of the test concentration.

Di(2-propylheptyl) phthalate is a peroxisome proliferator, although its effect is markedly weaker than that of di(2-ethylhexyl) phthalate. In a 13-week feeding study with rats, increased liver weights (relative weights in the males and absolute weights in the females) and an increase in the activity of cyanide-insensitive palmitoyl-CoA oxidase, the marker enzyme for peroxisome induction, were found after doses of

196 mg/kg body weight and day and above. In addition at this dose, changes in the thyroid and hypertrophy of the follicular tissue occurred, there was an increase in basophilic thyrotropic cells in the anterior lobe of the pituitary gland, serum albumin and the urine volume were increased, the haemoglobin level was decreased, and, in the male animals, also the haematocrit value.

In a 2-generation study with di(2-propylheptyl) phthalate in the diet, effects on the liver and kidneys were observed in rats after doses of 200 mg/kg body weight and day and above.

No adverse effects on the sexual organs of rats were observed in a 90-day feeding-study in which the animals were given di(2-propylheptyl) phthalate in doses of up to 1266 mg/kg body weight and day, or in a developmental toxicity study with doses up to 1000 mg/kg body weight and day, or in a 2-generation study with doses up to 600 mg/kg body weight and day.

In an oral 2-generation study with rats, no effects on fertility were observed up to doses of 600 mg/kg body weight and day. In a prenatal toxicity study with rats (gavage), there was an increase in soft tissue and skeletal variations, and early resorptions at 1000 mg/kg body weight and day; this dose was also slightly toxic to the dams.

Di(2-propylheptyl) phthalate was not found to be irritating to the skin or eyes of rabbits, nor sensitizing in a patch test with guinea pigs.

In vitro, di(2-propylheptyl) phthalate was not mutagenic in Salmonella typhimurium and in an HPRT test in CHO cells (a cell line derived from Chinese hamster ovary). The substance does not lead to chromosomal aberrations in V79 cells. There are no studies available for the in vivo genotoxicity and carcinogenicity of the substance.

2 Mechanism of Action

2.1 Mechanisms of the effects on the liver and kidneys

In the rat liver, di(2-propylheptyl) phthalate induces peroxisome proliferation. The activity of the marker enzyme for peroxisome proliferation, cyanide-insensitive palmitoyl-CoA oxidase, was increased in the 13-week feeding study with rats at the middle dose of 196 mg/kg body weight and day and above. This was accompanied by an increase in the absolute and relative liver weights and histological examination revealed hypertrophy of the liver cells in these animals (BASF AG 1995 d).

The slight nephrotoxicity found in both sexes in the 2-generation study, the eosinophilia in the proximal tubules and the increased kidney weights at 200 mg/kg body weight and day and above could be related to renal peroxisome proliferation (BASF SE 2009 b).

Peroxisome proliferation is mediated by the activation of the peroxisome proliferating receptor α (PPARα). In rodents, the increase in these cell organelles is accompanied by an increase in the incidence of mitosis in hepatocytes, which can be observed after only a few days. The liver remains enlarged during the entire exposure period as a result of the disturbance in hepatocyte growth control and the

inhibition of apoptosis. The breakdown of fatty acids is metabolically intensified, whereby an increased amount of H_2O_2 and heat is produced, unlike during mitochondrial fatty acid catabolism. In rodents, this metabolic situation can result in the development of liver carcinomas (Ashby et al. 1994; Cattley et al. 1998). It is necessary to distinguish, however, between weaker and stronger peroxisome proliferators. Indicators of later carcinogenic effects are, in particular, induction at low dose levels, pronounced organ enlargement, persistent cell proliferation and a long half-life of the agonists. Detailed descriptions of the effects produced by PPAR interaction can be found in the relevant documentation for di(2-ethylhexyl) phthalate and di-*n*-butyl phthalate (documentation "Di(2-ethylhexyl)phthalate (DEHP)" 2009; documentation "Di-n-butyl phthalate" 2013).

The data available at present indicate that the peroxisome proliferation in the liver of rodents activated by the PPARα receptor is generally of little relevance for humans. In in vitro studies conducted with primary hepatocytes, phthalic acid esters had no effects in guinea pigs and primates (Elcombe et al.1996). In addition, the PPARα receptor is found in the human liver in considerably lower concentrations (1% to 10%) than those found in the liver of rats and mice (Palmer et al. 1998).

2.2 Mechanisms of the effects on the thyroid and pituitary glands

In the 13-week study with rats, hypertrophy of the follicular epithelial cells in the thyroid gland and an increase in the number of basophilic (thyrotropic) cells in the anterior lobe of the pituitary gland were observed at doses of 196 mg/kg body weight and day and above (BASF AG 1995 d). In other studies with rats, similar effects were found with other phthalic acid esters (Hinton et al. 1986; Howarth et al. 2001; Poon et al. 1997; Price et al. 1988) and, in addition, reduced T4 levels in serum (Hinton et al. 1986). In humans, there is evidence of an inverse relationship between the urinary elimination of the di(2-ethylhexyl) phthalate metabolite monoethylhexyl phthalate (MEHP) and free T3 and T4 in serum (Meeker et al. 2007). In view of the high standard deviation, this still has to be confirmed in further studies, however. Whether this can be considered to be the sequel of phase II enzyme induction (with increased glucuronidation and the elimination of T3/T4 and subsequent stimulation of the hypothalamus–pituitary–thyroid gland axis) has, as yet, not been experimentally confirmed. In vitro, various phthalic acid esters also lead to a reduction in the uptake of iodine by thyroid follicle cells (Wenzel et al. 2005). No data for this are available for di(2-propylheptyl) phthalate.

In the case of thyroid gland stimulation as a result of a relative deficiency in T3/T4, pronounced differences are found between rats and humans (US EPA 1998).

While inductors of the xenobiotic metabolism in the liver are able to increase the TSH levels in rodents, it was shown in human studies with phenobarbital, rifampicin and other substances that although serum T4 concentrations may decrease, the TSH concentrations nevertheless remain in the normal range (Capen 2001; Curran and DeGroot 1991; Meek et al. 2003).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

There are no studies in humans available for the absorption of the substance after inhalation.

In a 5-day inhalation study with rats, there was an increase in the absolute and relative liver and lung weights at concentrations of 1000 mg/m^3 (BASF SE 2013), which indicates that the substance can be absorbed by inhalation.

Di(2-propylheptyl) phthalate is also absorbed via the oral route. In 1 male and 5 male volunteers given oral doses of 50 mg D4-labelled di(2-propylheptyl) phthalate (deuterium labelling on the aromatic ring), on average 24% to 34% of the dose was eliminated within 48 hours with the urine as specific degradation products (Leng et al. 2012; Wittassek and Angerer 2008). Also in rats, systemic effects were found in studies with repeated oral administration especially in the liver and thyroid gland (BASF AG 1995 d), so that absorption can be assumed. As this is not complete in humans (see above), also for rats only 50% oral absorption is assumed.

There are no studies available for the dermal penetration of di(2-propylheptyl) phthalate. Studies available with other phthalic acid esters show that the size of the molecules plays an important role. Therefore, studies with the isomer diisodecyl phthalate are used. In a study in rats with occlusive epicutaneous application for one day of 0.1 ml undiluted ^{14}C-labeled diisodecyl phthalate, corresponding to a dose of 5 to 8 mg/cm^2, 0.04% of the applied radioactivity was eliminated within 24 hours. 82% ± 12% of the radioactivity was recovered (Elsisi et al. 1989).From the 0.04% of the dose absorbed, an absorption rate of 0.13 µg/cm^2 and hour can be calculated; that means 0.26 mg is absorbed from an exposed area of skin of 2000 cm^2.

Furthermore, in vitro tests with undiluted di(2-ethylhexyl) phthalate show that the absorption rate in the steady state is 4 times higher in rats than for human skin (Scott et al. 1987, 1989). A similar difference can be expected also for di(2-propylheptyl) phthalate.

3.2 Metabolism

Humans

The aim of the studies with volunteers was not to obtain an overview of all the metabolites, but to identify a suitable urinary metabolite that can be used for biological monitoring.

After the ingestion of di(2-propylheptyl) phthalate by a volunteer, 34% of the dose was recovered in the urine within 61 hours in the form of the secondary metabolites mono(2-propyl-6-hydroxyheptyl) phthalate, mono(2-propyl-6-oxoheptyl) phthalate and mono(2-propyl-6-carboxyhexyl) phthalate. Less than 1% was eliminated with the urine in the form of mono(2-propylheptyl) phthalate. No information was given for other routes of elimination (faeces) (Wittassek and Angerer 2008).

In another study, single oral doses of about 50 mg D4-di(2-propylheptyl) phthalate were given to 5 male volunteers. Afterwards, individual urine samples were collected over a period of 48 hours. An average 24.7% of the dose was recovered in the urine within 48 hours, most of which (22.9%) was eliminated during the first 24 hours. Less than 1% of the dose was eliminated in the form of mono(2-propylheptyl) phthalate (MPHP). As secondary metabolites, 13.52% of the dose was eliminated with the urine as mono(2-propyl-6-oxoheptyl) phthalate (oxo-MPHP), 10.7% as mono(2-propyl-6-hydroxyheptyl) phthalate (OH-MPHP) and 0.5% as mono(2-propyl-6-carboxyhexyl) phthalate within 48 hours after administration (Leng et al. 2012, 2014).

Animals

There are no animal studies available for the kinetics and metabolism of di(2-propylheptyl) phthalate.

It can be assumed, however, that the extensively investigated kinetic profile of di(2-ethylhexyl) phthalate after oral administration also applies for di(2-propylheptyl) phthalate. After ingestion, the substance is accordingly cleaved to a large extent to form a semi-ester by the esterases in the small intestine. At this stage, the cleavage remains without further change; the second ester bond is, for steric or electrostatic reasons, no longer accessible to the enzyme. The molecule would therefore be absorbed as mono(2-propylheptyl) phthalate and then degraded from the end of the chain in the liver with the help of peroxisomal enzymes, during which process omega and omega-1-hydroxylation and their further oxidation and degradation products would dominate. These metabolites would be eliminated either directly or in glucuronated form with the urine and in part also be passed through enterohepatic circulation. Degradation to phthalic acid would occur in part, which, in turn, like the other metabolites, can be eliminated both with the urine and with the faeces (see documentation "Di(2-ethylhexyl)phthalate (DEHP)" 2009).

4 Effects in Humans

There are no studies available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

Five male and 5 female albino rats were exposed in whole-animal chambers for one hour to di(2-propylheptyl) phthalate aerosol in concentrations of 20.5 mg/l (20 500 mg/m^3; 3 to 5 µm MMAD; 100% dipropylheptyl phthalate isomers (containing 91.3% di(2-propylheptyl) phthalate)). Clinical symptoms were a wet coat and

piloerection, restlessness and breathing noises. The rats recovered after 24 hours. The observation period was 14 days. No deaths occurred, and histopathological examination did not yield any substance-related findings. The 1-hour LC_{50} for rats was greater than 20 500 mg/m³ (BASF SE 2009 a; ECHA 2014).

5.1.2 Oral administration

Groups of 5 male and 5 female fasting Sherman Wistar rats were given doses of 5000 mg di(2-propylheptyl) phthalate isomers/kg body weight (containing 91.3% di(2-propylheptyl) phthalate) by gavage. The recovery period was 14 days with daily observation. There were no deaths, no behavioural abnormalities or externally visible effects. The oral LD_{50} was greater than 5000 mg/kg body weight (BASF SE 2009 a; ECHA 2014).

5.1.3 Dermal application

A dose of 2000 mg di(2-propylheptyl) phthalate isomers/kg body weight (containing 91.3% di(2-propylheptyl) phthalate) was applied to the dorsal skin of 3 male and 5 female albino rats, and the area was covered with gauze. Excess substance and the gauze were removed after 24 hours. There were no deaths, no noticeable changes in behaviour or gross pathological findings. The dermal LD_{50} in the rat was greater than 2000 mg/kg body weight (BASF SE 2009 a; ECHA 2014).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a 5-day inhalation study, groups of 10 male Wistar rats were exposed to di(2-propylheptyl) phthalate aerosol in concentrations of 0, 50, 250 or 1000 mg/m³ for 6 hours a day. The dew point, which designates the transition from the vapour phase to an aerosol, is 0.0007 mg/m³ in the case of di(2-propylheptyl) phthalate and thus far below the lowest test concentration; aerosols were therefore present at all exposure concentrations. The highest concentration of 1000 mg/m³ led to an increase in the absolute and relative liver (+30%) and lung weights (+37%). The following secondary effects can be seen as sequels of the overloading of the lungs and macrophages with the oily, insoluble material: foam cell infiltrations in the terminal bronchioles and slight to moderate alveolar histiocytosis, combined with a slight to moderate lymphoreticular reaction in the mediastinal lymph nodes. In addition, there was slight to moderate hypertrophy in the terminal bronchial epithelium and in the trachea. These effects, although much weaker, could be observed also at 250 mg/m³, but not at 50 mg/m³. Independent of this, exposure to di(2-propylheptyl) phthalate aerosol produced goblet cell hyperplasia, the increased presence of goblet cells in plane of section III of the nasal conchae, in all concentration groups and in all exposed animals, but not in the controls. At the high concentration of 1000 mg/m³,

the formation of mucus was increased, and hypertrophy of the goblet cells was found in 7 of 10 animals. Effects, for which severity levels were established, were found in the lungs, trachea, liver, mediastinal lymph nodes and tracheobronchial lymph nodes, but not in the nose. Only in the lungs were the following effects observed also in the middle concentration group: grade 1 inflammation, grade 2 histiocytosis and grade 1 and 2 bronchiolar hyperplasia (BASF SE 2013, 2014; ECHA 2014). The increased presence of goblet cells is a physiological reaction to an overload phenomenon as a reaction to the impaction of the oily particles and does not represent a substance-specific adverse effect, but is an adaptive process, resulting in proliferative effects. The increased differentiation of stem cells in the basal epithelial layer to form goblet cells (instead of cylinder cells) is a physiological process that serves to produce more mucus as a reaction to the aerosol impaction, which is reversible over a long period of time (Renne et al. 2009; Rogers 1994). However, it is not known how such findings develop over longer exposure periods.

In this 5-day study with di(2-propylheptyl) phthalate, no effects on the larynx occurred, such as had been found with di-*n*-butyl phthalate in a 28-day inhalation study (documentation "Di-n-butyl phthalate" 2013). As there were no clinical findings after exposure to di(2-propylheptyl) phthalate, adverse effects on the larynx are probably not to be expected. This can, however, not be confirmed on the basis of the available data. It can be assumed from the grade 1, squamous cell-like metaplasia in the larynx following exposure to di-*n*-butyl phthalate that these effects do not increase in severity even after long-term exposure. This can be assumed from the flat dose–response relationship obtained in the 28-day inhalation study with di-*n*-butyl phthalate, and was additionally confirmed in 2 and 13-week inhalation studies with glycerol (Renne et al. 1992) and in inhalation studies with butynediol (documentation "2-Butin-1,4-diol" 2012, available in German only). For the latter two substances, the severity of the grade 1 to 2 squamous cell-like metaplasia in the larynx did not increase in inhalation studies over the course of the exposure period. Squamous cell metaplasia in the larynx of grade 1 to 2 is regarded as an adaptive effect (Kaufmann et al. 2009), and therefore not used for the derivation of the MAK value.

The chemically similar phthalate, di(2-ethylhexyl) phthalate, which does not differ greatly from di(2-propylheptyl) phthalate as regards its physico-chemical properties and membrane permeability, was investigated earlier in a 28-day inhalation study in rats given concentrations of 0, 10, 50 or 1000 mg/m^3. Concentrations of 1000 mg/m^3 led to increased lung and liver weights. No effects were observed after 50 mg/m^3. The nasal cavities (4 planes of section) were also investigated, but no adverse effects were found. No information is given regarding an increase in goblet cells (Klimisch et al. 1992). In addition, over the 20-year period, the findings were not recorded in exactly the same manner. Neither was the larynx histologically examined in this study. It can be assumed that dose-dependently increasing effects in the larynx would have become clinically visible at 1000 mg/m^3. It was reported in a review that larynx metaplasia of mild severity can also be induced by particles in the inhaled air after dehydration by alcohols or by dry air (Osimitz et al. 2007).

Summary

In the 5-day inhalation study with male rats, **di(2-propylheptyl) phthalate** produced grade 1 to 2 goblet cell hyperplasia in plane of section III of the nasal conchae only in the exposed animals at the lowest exposure concentration of 50 mg/m³ and above. No effects were found in the larynx or in other target organs. In a 28-day inhalation study with **di(2-ethylhexyl) phthalate**, a no observed adverse effect concentration (NOAEC) of 50 mg/m³ is given; the study report gives no details regarding goblet cells, the larynx was not investigated (Klimisch et al. 1992). In a 28-day inhalation study with rats exposed to **di-*n*-butyl phthalate** concentrations of 1.18 mg/m³, grade 1 to 2 goblet cell hyperplasia and grade 1 larynx metaplasia were found in planes of section II to IV of the nasal conchae (documentation "Di-n-butyl phthalate" 2013). Larynx metaplasia is not regarded as an adverse effect up to grade 2 (Kaufmann et al. 2009). The development of these effects after prolonged exposure periods is not clear, however. From inhalation studies with glycerol (2 and 13 weeks; Renne et al. 1992) and butynediol (documentation "2-Butin-1,4-diol" 2012, available in German only) it can be concluded that the grade 1 to 2 larynx metaplasia does not change in severity even after prolonged exposure. Larynx metaplasia at this level of severity does not therefore need to be taken into account for the derivation of a MAK value. There are no investigations and comparative studies available for the development of goblet cell hyperplasia after prolonged exposure. No statement can be made as to whether the grade 1 to 2 goblet cell hyperplasia develops into higher levels of severity after prolonged exposure; if this should be the case, it would then have to be taken into consideration for the derivation of a MAK value.

5.2.2 Oral administration

In a range-finding study, groups of 5 male and 5 female Wistar rats were given doses of 0, 1000, 10 000 or 20 000 ppm di(2-propylheptyl) phthalate with the diet (0, 92, 920 or 1500 mg/kg body weight and day for the males and 0, 100, 1020 or 2050 mg/kg body weight and day for the females) for 14 days. At the high dose, food consumption and body weights were decreased by 17% in the male rats and by 9% in the females. In this dose group, piloerection was observed in 2 animals per sex. In the animals of the middle and high dose groups, the activity of cyanide-insensitive palmitoyl-CoA oxidase in the liver was increased. At the low dose of 92 or 100 mg/kg body weight and day, no substance-specific effects occurred (BASF AG 1995 d).

In the subsequent 13-week study carried out according to OECD Test Guideline 408, groups of 10 female and 10 male rats were given concentrations of 0, 500, 2500 or 15 000 ppm di(2-propylheptyl) phthalate (corresponding to 0, 39, 196 or 1266 mg/kg body weight and day) with the diet. In the high dose group, there was a decrease in body weights up to day 91 of 6% and 8% in females and males, respectively, and in body weight gains of 11% and 17%; in addition, the absolute and relative liver weights were increased. In the middle dose group, the relative liver weights were increased in the male rats and the absolute liver weights in the females. In the two high dose groups, peroxisome proliferation and liver cell hypertrophy were observed. The cya-

nide-insensitive palmitoyl-CoA oxidase level was increased 8 to 10-fold throughout in the high dose group. In the middle dose group the increase was 1.5-fold (significant only in the female animals). In 8 male rats of the high dose group, there was an increase in basophilic (thyrotropic) cells in the anterior lobe of the pituitary gland. Hypertrophy of the follicular thyroid gland tissue was found in both sexes. In the middle dose group, the changes in the pituitary gland could be found in 3 males and the follicular effects in 8 male and 4 female animals. Effects on the reproductive organs were not found in any of the dose groups. Clinico-chemical investigations revealed decreased serum triglycerides in the males at the high dose and decreased serum glucose levels in females. This is associated with the lipid-lowering effects of peroxisome proliferation. In addition, there was an increase in serum albumin and the urine volume in both sexes, a decrease in haemoglobin and, in the male rats, in the haematocrit value; creatinine levels were increased in the females (BASF AG 1995 d; ECHA 2014). The latter could indicate slight kidney damage, as was found also in the 2-generation study, where increased kidney weights were determined in the males at 600 mg/kg body weight. In this oral 13-week study with rats, the no observed adverse effect level (NOAEL) was 39 mg/kg body weight and day.

In a study carried out in 1997, di(2-propylheptyl) phthalate doses of 0, 40, 420 or 1000 mg/kg body weight and day were given to groups of 12 male and 12 female rats with the diet for 14 weeks. Some of the animals from the control group and the high dose group were observed for another 4 weeks (recovery period). There was a dose-dependent increase in liver weights and in the enzymes of peroxisome proliferation in all exposed animals, which was not significant at the low dose. At doses of 420 mg/kg body weight and day and above, the cyanide-insensitive palmitoyl-CoA oxidase level was increased and the resulting signs of liver damage could be seen; at the same time, the serum triglycerides were decreased, as were the haemoglobin and haematocrit levels. Food consumption was reduced at 1000 mg/kg body weight and day and the body weight gains were reduced by about 20%. The NOAEL was 40 mg/kg body weight and day (ECHA 2014).

5.2.3 Dermal application

There are no studies available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In accordance with OECD Test Guideline 404, 0.5 ml di(2-propylheptyl) phthalate isomers (sum of isomers: 99.2%, containing 80.9% di(2-propylheptyl) phthalate) was applied semi-occlusively to the intact skin of the flanks of 3 New Zealand White rabbits for 4 hours. The application site was examined after 1, 24, 48 and 72 hours. Slight erythema was found (maximum score 0.1 of 4) one hour after application in all animals which, however, had completely regressed after 48 hours at

the latest. Under these conditions, di(2-propylheptyl) phthalate was regarded as non-irritating (BASF AG 2002 a; ECHA 2014).

In another study, under occlusive conditions, 0.5 g di(2-propylheptyl) phthalate isomers (containing 91.3% di(2-propylheptyl) phthalate) was applied once to the shaved dorsal skin and once to the abraded dorsal skin of 3 albino rabbits in each case and covered with gauze. The gauze was removed 24 hours after application and the treated site was evaluated using the Draize scale for erythema, eschar formation and oedema. A second examination was carried out 72 hours later. Di(2-propylheptyl) phthalate did not lead to erythema or oedema at any time, and it was regarded as non-irritating (BASF SE 2009 a; ECHA 2014).

5.3.2 Eyes

In accordance with OECD Test Guideline 405, 0.1 ml di(2-propylheptyl) phthalate isomers (sum of isomers: 99.2%, containing 80.9% di(2-propylheptyl) phthalate) was instilled into one eye of 3 New Zealand White rabbits. The test substance was washed off after 24 hours. Slight to moderate reddening of the conjunctiva with a maximum average score of 0.3 on a scale up to 3 and slight lacrimation occurred. These reactions were reversible after 48 hours. In this study, di(2-propylheptyl) phthalate was not irritating to the eyes (BASF AG 2002 b; ECHA 2014).

In an earlier study, 0.1 g di(2-propylheptyl) phthalate isomers (containing 91.3% di(2-propylheptyl) phthalate) was instilled into the right eye of 6 albino rabbits. The test substance was not washed off. The eyes were examined over a period of up to 7 days after the instillation. Di(2-propylheptyl) phthalate did not produce reactions at any time, and under these study conditions was not irritating to the eyes (BASF SE 2009 a; ECHA 2014).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

The contact sensitization potential of di(2-propylheptyl) phthalate isomers (containing 91.3% di(2-propylheptyl) phthalate) was investigated in an occlusive patch test in only 5 female and 5 male albino guinea pigs. The animals were treated on alternating days with ten 24-hour occlusive applications consisting of 0.5 g of the undiluted test substance. After a 2-week interval, a challenge test with another 24-hour application of the undiluted substance took place. No reaction occurred in any of the animals after 24 or 48 hours (BASF SE 2009 a; ECHA 2014).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a 2-generation study carried out according to OECD Test Guideline 416, di(2-propylheptyl) phthalate was administered with the diet in doses of 0, 40, 200 or 600 mg/kg body weight and day to 25 male and 25 female Wistar rats. In animals of the F0 generation given 600 mg/kg body weight and day, food consumption was reduced and body weight gains were delayed. Absolute and relative liver weights were increased in both sexes, absolute and relative kidney weights only in the male animals. These effects were observed also in the F1 parents. Hepatocellular hypertrophy and peroxisome proliferation were histologically determined in the F0 animals. In the F0 and F1 parents, clinical laboratory examinations revealed increases in transaminases and alkaline phosphatase, furthermore a reduction in triglycerides and cholesterol. The increase in urea and several anaemic effects (decreased haemoglobin, haematocrit and erythrocyte counts) occurred in association with renal effects. In the F1 generation, the body weight gains were reduced in the parents at 600 mg/kg body weight and day and the thyroid weights were increased in the female animals. Histological examination yielded follicular hyperplasia or hypertrophy in 16 male and 18 female animals. The number of basophilic cells in the anterior lobe of the pituitary gland was increased in 7 male animals. In the F0 generation given 200 mg/kg body weight and day, the same effects were observed, but of weaker severity. Effects on the liver and kidneys were found in the F1 parents of the middle dose group; these were more pronounced than in the F0 generation. The body weights of the offspring of the F1 and F2 generations were reduced from day 14 and the body weight gains were reduced from day 4 or 7 up to weaning. Morphologically, there were no substance-related adverse effects in the offspring of the F1 and F2 generations. The dose of 40 mg/kg body weight and day did not cause substance-related effects in either the F0 or F1 parent generations or in the offspring of the F1 and F2 generations. In all, this study demonstrated the subchronic effects on the liver, kidneys and thyroid already known for di(2-propylheptyl) phthalate. However, neither the fertility nor the reproductive parameters were affected, nor viability, the sex ratio or sexual development. There were no irregularities in the anogenital distance or in the anogenital index or the number of areolae in the males of the F1 and the F2 generations (BASF SE 2009 b; ECHA 2014). The NOAEL for systemic toxicity was therefore 40 mg/kg body weight and day, as found also in the preceding medium-term study. The NOAEL for fertility was the high dose of 600 mg/kg body weight and day. There were no adverse effects on fertility or the offspring even in the higher dose range, where effects on the target organs liver, kidneys and thyroid gland were found.

5.5.2 Developmental toxicity

In a range-finding study, 10 pregnant Wistar rats were given gavage doses of di(2-propylheptyl) phthalate in olive oil of 0, 40, 200 or 1000 mg/kg body weight and day on

days 6 to 15 of gestation (OECD Test Guideline 414). Necropsy was carried out on day 20 of gestation. Up to the highest dose, no substance-related effects on the dams were found regarding body weights, food consumption, the weights of the liver, kidneys and uterus, clinico-chemical parameters and gross pathological findings. There were no biologically relevant differences between the controls and rats treated with the substance regarding the incidence of pregnancy, the average number of corpora lutea, the total number of implantations, resorptions, live foetuses, pre and post-implantation losses and placental weights. In the foetuses, there were no effects on body weights and the sex ratio. External examinations and investigation of the soft tissue or skeleton of the foetuses did not reveal any differences between the controls, including historical controls, and the treated animals (BASF AG 1995 c; ECHA 2014).

In the subsequent prenatal developmental toxicity study carried out according to OECD Test Guideline 414, gavage doses of di(2-propylheptyl) phthalate in olive oil of 0, 40, 200 or 1000 mg/kg body weight and day were administered to groups of 25 pregnant Wistar rats on days 6 to 19 of gestation. This study, therefore, covers the critical period for the effects of several phthalates from days 16 to 18 of gestation (Carruthers and Foster 2005). In the low and middle dose groups, no substance-related effects on the dams, the pregnancy parameters or the foetuses were found. At 1000 mg/kg body weight and day, urine contaminated fur was observed in 5 pregnant rats on days 16 to 20 of gestation, from which an impairment in the well-being of the dams can be concluded. Food consumption was decreased by 11% throughout the entire treatment period, the mean body weights were decreased by 6% on day 20 of gestation and the corrected body weight gains were decreased by 30% compared with in the control group. The mean uterus weights were decreased by 19% compared with those in the controls; 3 animals had no litters, only very early resorptions. The post-implantation losses therefore increased to 23.1% compared with 6.2% in the control group. A slight, but significantly increased number of foetuses with variations such as dilation of the renal pelvis or ureter, non-ossified sternebrae and additional ribs was recorded. The decreased body weights in the high dose group at the beginning of the treatment, which was accompanied by reduced food consumption, indicates adverse effects on the dams with a simultaneous increase in early resorptions. At this early point in pregnancy, the weights of the embryos or foetuses make only a negligible contribution to the body weights of the dams. Only the reduced body weights on days 19 to 20 of gestation and the reduced uterus weights at 1000 mg/kg body weight and day are associated with the increased incidence of resorption (BASF AG 2003; ECHA 2014). In this study, the NOAEL for maternal and developmental toxicity was 200 mg/kg body weight and day.

5.6 Genotoxicity

5.6.1 In vitro

In two mutation tests with Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537, no increase in his^+ revertants was found up to di(2-propylheptyl)

phthalate concentrations of 5 mg/plate in either the absence or presence of a metabolic activation system. Under these conditions, di(2-propylheptyl) phthalate was therefore not mutagenic (BASF AG 1995 b; ECHA 2014).

In V79 cells, di(2-propylheptyl) phthalate did not induce chromosomal aberrations in the absence and presence of a metabolic activation system and therefore does not have clastogenic effects up to the highest concentration tested of 5.2 mg/ml (BASF SE 2010 a; ECHA 2014).

In the HPRT test with CHO cells, di(2-propylheptyl) phthalate did not induce point mutations in either the absence or presence of a metabolic activation system up to the highest concentration tested of 5.2 mg/ml. At concentrations of 0.65 mg/ml and above, some of the substance precipitated from the solution (BASF SE 2010 b; ECHA 2014).

Conclusion

In vitro, di(2-propylheptyl) phthalate does not have genotoxic effects in bacteria and mammalian cells.

5.6.2 In vivo

There are no in vivo studies available for the genotoxicity of the substance.

5.7 Carcinogenicity

There are no data available for the carcinogenicity of di(2-propylheptyl) phthalate.

The NOAEL for peroxisome proliferation in the 90-day study was di(2-propylheptyl) phthalate doses of 39 mg/kg body weight and day. At 196 mg/kg body weight and day, the activity of cyanide-insensitive palmitoyl-CoA oxidation in the rat liver was increased by a factor of 1.5. A 2 to 4-fold increase was found after di(2-ethylhexyl) phthalate doses of 100 mg/kg body weight and day, and in animals aged between 14 and 18 days even at doses as low as 10 mg/kg body weight and day (Dostal et al. 1987). Aged rats are possibly more sensitive to peroxisome-related tumour promotion (Kraupp-Grasl et al. 1991). Although carcinogenicity has not been demonstrated for di(2-propylheptyl) phthalate, it can also not be excluded.

6 Manifesto (MAK value/classification)

Di(2-propylheptyl) phthalate is not irritating to the eyes of rabbits. The local effects on the respiratory tract (which, for example, after aerosol exposure to di-*n*-butyl phthalate lead to larynx metaplasia and goblet cell hyperplasia) cannot be estimated for di(2-propylheptyl) phthalate as only one 5-day inhalation study is available. The critical effect for the evaluation of its systemic toxicity is peroxisome proliferation in rat liver after oral administration.

Carcinogenicity. There are no carcinogenicity studies with di(2-propylheptyl) phthalate available. Di(2-ethylhexyl) phthalate, which is similar in structure, was found to be carcinogenic in the rat liver in long-term studies. It is known from studies of the mechanism of action and an oral 13-week study with rats that di(2-propylheptyl) phthalate induces peroxisome proliferation in the liver, which is, however, less pronounced than that caused by the structurally related di(2-ethylhexyl) phthalate. In view of the similar mechanism of action of di(2-ethylhexyl) phthalate, which is classified in Carcinogen category 4, and the fact that carcinogenicity after long-term exposure is suspected although no study exists, di(2-propylheptyl) phthalate is classified in Carcinogen category 3B.

Germ cell mutagenicity. In vitro, di(2-propylheptyl) phthalate was not found to be genotoxic in bacteria and mammalian cells. In vivo studies are not available. Phthalates with a similar structure are not genotoxic in vivo. The substance is therefore not classified in one of the categories for germ cell mutagens.

MAK value and peak limitation. In a 13-week feeding study with rats, the NOAEL for systemic toxicity was 39 mg di(2-propylheptyl) phthalate/kg body weight and day. Peroxisome proliferation in the liver occurred at 196 mg/kg body weight and day. In addition, effects on the kidneys and hypertrophy of the follicular thyroid gland tissue, combined with changes in the pituitary gland and increased basophilic or thyrotropic cells were found. The following toxicokinetic data are taken into consideration for the extrapolation of the oral NOAEL in rats to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction values for the rat (1:4), the assumed oral absorption of 50%, the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 48 mg/m^3. This concentration seems to be too high, as local effects on the respiratory tract have been found with other phthalates at lower concentrations.

To estimate the local toxicity in the respiratory tract after inhalation of di(2-propylheptyl) phthalate aerosol, a 5-day inhalation study is available in which grade 1 goblet cell hyperplasia occurred in plane of section III of the nasal conchae as the only finding at the low concentration of 50 mg/m^3. Increased lung weights with inflammatory infiltrates and with epithelial hyperplasia in the terminal bronchioles occurred at concentrations of 250 and 1000 mg/m^3 (BASF SE 2013). No larynx metaplasia occurred, such as was found with a severity of grade 1 after the exposure of rats to di-*n*-butyl phthalate for 28 days. As described in Section 5.2.1, the severity of the metaplasia in the larynx does not change after prolonged exposure. As grade 1 goblet cell hyperplasia was found, however, after the 28-day exposure of rats to the physico-chemically similar di-*n*-butyl phthalate, and the development of this with long-term exposure is not known, the local effects of di(2-propylheptyl) phthalate in the respiratory tract cannot be assessed. Because of the very short exposure duration of only 5 days, a MAK value cannot be derived from this study, and peak limitation is not applicable.

Prenatal toxicity. No specifically foetal effects were found in a study carried out according to OECD Test Guideline 414 in rats. The highest di(2-propylheptyl)

phthalate dose tested was 1000 mg/kg body weight and day, maternal toxicity was observed at 200 mg/kg body weight and day. Also in a 2-generation study, no adverse effects on litter parameters and foetuses were observed up to doses of 600 mg/kg body weight and day. As no MAK value can be derived, classification in one of the pregnancy risk groups is not applicable.

Absorption through the skin. There are no data available for di(2-propylheptyl) phthalate. The absorption through the skin of phthalates with higher chain lengths (> 4 C atoms) and branching is very low. From a study in rats with the isomer diisodecyl phthalate, an average absorption rate of 0.13 μg/cm² and hour can be calculated. The exposure of 2000 cm² for 1 hour would result in a dose of 0.26 mg per 70 kg body weight corresponding to 0.004 mg/kg body weight in humans. This dose is considerably lower than the systemic NOAEL of 40 mg/kg body weight in the 13-week study, equivalent to a calculated dose of 7 mg/kg body weight in humans. Di(2-propylheptyl) phthalate is therefore not designated with an "H" (for substances which can be absorbed through the skin).

Sensitization. There are no clinical findings available for sensitizing effects of the substance on the skin or respiratory tract. An occlusive patch test with only 10 guinea pigs yielded a negative result with the undiluted substance. There are no studies with experimental animals available for sensitizing effects on the airways. Di(2-propylheptyl) phthalate is therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

7 References

Ashby J, Brady A, Elcombe CR, Elliott BM, Ishmael J, Odum J, Tugwood JD, Kettle S, Purchase IFH (1994) Mechanistically-based human hazard assessment of peroxisome-proliferator-induced hepatocarcinogenesis. Hum Exp Toxicol 13: S1–S117

BASF AG (Badische Anilin- und Soda-Fabrik) (1995 a) Physikalisch-chemische Stoffwerte von Dipropylheptylphthalat (Physico-chemical values for Dipropylheptylphthalate) (German). BASF AG Ludwigshafen, GLP Order No.: 94L00318, 29 March 1995, BASF AG, Ludwigshafen, unpublished report

BASF AG (1995 b) Report on the study of Dipropylheptylphthalate in the Ames Test (Salmonella/Mammalian-Microsome mutagenicity test – standard plate test and preincubation test), BASF AG, Project No. 40M0110/944241, 3 July 1995, BASF AG, Ludwigshafen, unpublished

BASF AG (1995 c) Study of the prenatal toxicity of Dipropylheptylphthalate in Wistar rats after oral administration (gavage), screening. BASF AG, Project No. 10R0110/94013, 3 April 1995, BASF AG, Ludwigshafen, unpublished report

BASF AG (1995 d) Subchronic oral toxicity study with Dipropylheptylphthalate in Wistar rats, administration in the diet for 3 months. BASF AG, Project No. 50C0110/94025, 21st December 1995, BASF AG, Ludwigshafen, unpublished report

BASF AG (1995 e) Dampfdruck und Siedebereich (Vapour pressure and boiling point) (German). BASF AG, Report BRU 95.395, 21.9.1995, BASF AG, Ludwigshafen, unpublished

BASF AG (1999) Dampfdruck von CAS-Nr. 53306-54-0 (Vapour pressure of CAS No. 53306-54-0) (German). BASF AG, Report 99.295.3, BASF AG, Ludwigshafen, unpublished

BASF AG (2000 a) Pourpoint. BASF AG, LZC/WT-H200, 18.10.2000, BASF AG, Ludwigshafen, unpublished report

BASF AG (2002 a) Acute dermal irritation/corrosion in rabbits. BASF AG, Project No. 18H0183/022042, 11 September 2002, Amendment 2 April 2003, BASF AG, Ludwigshafen, unpublished report

BASF AG (2002 b) Acute eye irritation in rabbits. BASF AG, Project No. 11H0183/022043, 11 September 2002, Amendment: April 2, 2003, BASF AG, Ludwigshafen, unpublished report

BASF AG (2003) Prenatal developmental toxicity study in Wistar rats – oral administration (gavage). BASF AG, Project No. 30R0183/02046, 24 November 2003, BASF AG, Ludwigshafen, unpublished report

BASF SE (2009 a) Substance 53306-54-0 master bis(2-propylheptyl)phthalate (IUC4 DSN 4). EU REACH, BASF SE, Ludwigshafen, unpublished report

BASF SE (2009 b) Two-generation reproduction toxicity study in Wistar rats – administration via the diet. BASF SE, Project No. 70R0183/02087, 2nd November 2009, BASF SE, Ludwigshafen, unpublished report

BASF SE (2010 a) In vitro chromosome aberration assay in V79 cells. BASF SE, Project No. 32M0183/02M001, 7th October 2010, Amendment 11th February 2011, BASF SE, Ludwigshafen, unpublished report

BASF SE (2010 b) In vitro gene mutation test in CHO cells (HPRT locus assay). BASF SE, Project No. 50M0183/02M002, 6th September 2010, BASF SE, Ludwigshafen, unpublished report

BASF SE (2013) Summary Report 5-day inhalation toxicity study in male wistar rats; liquid aerosol exposure. BASF SE, Project No. 30I0183/02I017, 14th February 2013, BASF SE, Ludwigshafen, unpublished

BASF SE (2014) Verwendung, Herstellung und Zusammensetzung von Di(2-propylheptyl) phthalat (Uses, production and composition of di(2-propylheptyl) phthalate) (German). Communication to the Commission from Dr. Otter on 3.9.2014

Capen CC (2001) Overview of structural and functional lesions in endocrine organs of animals. Toxicol Pathol 29: 8–33

Carruthers CM, Foster P (2005) Critical window of male reproductive tract development in rats following gestational exposure to di-n-butyl phthalate. Birth Defects Res B Dev Reprod Toxicol 74: 277–285

Cattley RC, DeLuca J, Elcombe C, Fenner-Crisp P, Lake BG, Marsman DS, Pastoor TA, Popp J, Robinson DE, Schwetz B, Tugwood J, Wahli W (1998) Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? Regul Toxicol Pharmacol 27: 47–60

Curran PG, DeGroot LJ (1991) The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. Endocr Rev 12:135–150

Dostal LA, Jenkins WL, Schwetz BA (1987) Hepatic peroxisome proliferation and hypolipidemic effects of di(2-ethylhexyl)phthalate in neonatal and adult rats. Toxicol Appl Pharmacol 87: 81–90

ECHA (European Chemical Agency) (2014) Information on registered substances. Dataset on bis(2-propylheptyl) phthalate (CAS number53306-54-0), http://echa.europa.eu/web/guest/information-on-chemicals

Elcombe CR, Bell DR, Elias E, Hasmall SC, Plant NJ (1996) Peroxisome proliferators: species differences in response of primary hepatocytes cultures. Ann NY Acad Sci 804: 628–635

Elsisi AE, Carter DE, Sipes IG (1989) Dermal absorption of phthalate diesters in rats. Fundam Appl Toxicol 12: 70–77

Hinton RH, Mitchell FE, Mann A, Chescoe D, Price SC, Nunn A, Grasso P, Bridges JW (1986) Effects of phthalic acid esters on the liver and thyroid. Environ Health Perspect 70: 195–210

Howarth JA, Price SC, Miloslav D, Kentish PA, Hinton RH (2001) Effects on male rats of di(2-ethylhexy) phthalate and di-n-hexylphthalate administered alone or in combination. Toxicol Lett 121: 35–43

Kaufmann W, Bader R, Ernst H, Harada T, Hardisty J, Kittel B, Kolling A, Pino M, Renne R, Rittinghausen S, Schulte A, Wöhrmann T, Rosenbruch M (2009) 1st International ESTP Expert Workshop: "Larynx squamous metaplasia". A re-consideration of morphology and diagnostic approaches in rodent studies and its relevance for human risk assessment. Exp Toxicol Pathol 61: 591–603

Klimisch HJ, Gamer AO, Hellwig J, Kaufmann W, Jäckh R (1992) Di(2-ethylhexyl)phthalate: a short-term repeated inhalation toxicity study including fertility assessment. Food Chem Toxicol 30: 915–919

Kraupp-Grasl B, Huber W, Taper H, Schulte-Hermann R (1991) Increased susceptibility of aged rats to hepatocarcinogenesis by the peroxisome proliferator Nafenopin and the possible involvement of altered liver foci occurring spontaneously. Cancer Res 51: 666–671

Leng G, Gries W, Koch H (2012) Entwicklung einer Analysenmethode zum Nachweis von DPHP (Bis(2-Propylheptyl)phthalat) in der Allgemeinbevölkerung (Development of an analytical method for detecting DPHP (bis(2-propylheptyl)phthalate) in the general population) (German). 52. Wissenschaftliche Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (52nd Annual scientific meeting of the German Society for Occupational and Environmental Medicine), 14–17 March 2012, Göttingen, http://www.dgaum.de/fileadmin/PDF/Tagungsbaende/DGAUM_Tagungsband_2012.pdf

Leng G, Koch HM, Gries W, Schütze A, Langsch A, Brüning T, Otter R (2014) Urinary metabolite excretion after oral dosage of bis(2-propylheptyl)phthalate (DPHP) to five male volunteers – characterization of suitable biomarkers for human biomonitoring. Toxicol Lett 231: 282–288

Meek ME, Bucher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD, Longfellow DG, Pastoor T, Seed J, Patton DE (2003) A framework for human relevance analysis of information on carcinogenic modes of action. Crit Rev Toxicol 33: 591–653

Meeker JD, Calafat AM, Hauser R (2007) Di(2-ethylhexyl) phthalate metabolites may alter thyroid hormone levels in man. Environ Health Perspect 115: 1029–1034

Osimitz TG, Droege W, Finch JM (2007) Toxicological significance of histologic change in the larynx of the rat following inhalation exposure: a critical review. Toxicol Appl Pharmacol 225: 229–237

Palmer CAN, Hsu MH, Griffin KJ, Raucy JL, Johnson EF (1998) Peroxisome proliferator activated receptor-α expression in human liver. Mol Pharmacol 53: 14–22

Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG, Chu I (1997) Subchronic oral toxicity of Di-n-octylphthalate and Di(2-ethylhexyl)phthalate in the rat. Food Chem Toxicol 35: 225–239

Price SC, Chescoe D, Grasso P, Wright M, Hinton RH (1988) Alterations in the thyroids of rats treated for long periods with Di(2-ethylhexyl) phthalate or with hypolipidaemic agents. Toxicol Lett 40: 37–46

Renne RA, Wehner AP, Greenspan BJ, DeFord HS, Ragan HA, Westerberg RB, Buschbom RL, Burger GT, Hayes AW, Suber RL, Mosberg AT (1992) 2-Week and 13-week inhalation studies of aerosolized glycerol in rats. Inhal Toxicol 4: 95–111

Renne R, Brix A, Harkema J, Herbert R, Kittel B, Lewis D, March T, Nagano K, Pino M, Rittinghausen S, Rosenbruch M, Tellier P, Wohrmann T (2009) Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. Toxicol Pathol 37: 5S–73S

Rogers DF (1994) Airway goblet cells: responsive and adaptable front-line defenders. Eur Respir J 7: 1690–1706

Scott RC, Dugard PH, Ramsey JD, Rhodes C (1987) In vitro absorption of some o-phthalate diesters through human and rat skin. Environ Health Perspect 74: 223–227

Scott RC, Dugard PH, Ramsey JD, Rhodes C (1989) Errata to "Scott RC, Dugard PH, Ramsey JD, Rhodes C (1987) In vitro absorption of some o-phthalate diesters through human and rat skin. Environ Health Perspect 74: 223–227". Environ Health Perspect 79: 323

US EPA (Environmental Protection Agency) (1998) Assessment of thyroid follicular cell tumors, US EPA, EPA/630/R-97/002, March 1998, Washington, USA, http://www.epa.gov/raf/publications/pdfs/THYROID.PDF

Wenzel A, Franz C, Beous E, Loos U (2005) Modulation of iodide uptake by dialkyl phthalate plasticisers in FRTL-5 rat thyroid follicular cells. Mol Cell Endocrinol 244: 63–71

Wittassek M, Angerer J (2008) Phthalates: metabolism and exposure. Int J Androl 31: 131–138

completed 16.12.2013