The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

n-Butylbenzene

MAK Value Documentation – Translation of the German version from 2018

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, Building 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

n-butylbenzene; kidney; liver; hepatocellular hypertrophy; MAK value; maximum workplace concentration; skin absorption

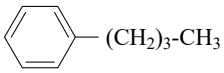
Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated *n*-butylbenzene [104-51-8], considering all toxicological endpoints. Available publications are described in detail. In an oral two-generation study in rats, increased kidney weights and centrilobular hypertrophy in the liver is observed with *n*-butylbenzene. The corresponding NOAEL of 100 mg/kg body weight and day is scaled to a maximum concentration at the workplace (MAK value) of 10 ml/m^3. Studies on the possible irritation of the airways after repeated inhalation exposure are lacking, however, the acute RD_{50} value of 710 ml/m^3 in mice is indicative of an irritation threshold of about 20 ml/m^3 in humans. Therefore, the systemic effect is critical and Peak Limitation Category II is designated. As the half-life of *n*-butylbenzene is not known, the default excursion factor of 2 for systemically acting substances is established. There are no developmental toxicity studies. Therefore, *n*-butylbenzene is assigned to Pregnancy Risk Group D. There are no data on genotoxicity, carcinogenicity and sensitization. According to skin absorption models, percutaneous absorption can contribute significantly to systemic toxicity and *n*-butylbenzene is designated with an "H" notation.

Citation Note:
Hartwig A, MAK Commission. *n*-Butylbenzene. MAK Value Documentation – Translation of the German version from 2018. MAK Collect Occup Health Saf. 2022 Sep;7(3):Doc050. https://doi.org/10.34865/mb10451e7_3or

Manuscript completed:
20 Mar 2017

Publication date:
30 Sep 2022

MAK value (2017)	**10 ml/m³ (ppm) ≙ 56 mg/m³**
Peak limitation (2017)	**Category II, excursion factor 2**
Absorption through the skin (2017)	**H**
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2017)	**Pregnancy Risk Group D**
Germ cell mutagenicity	–
BAT value	–
Synonyms	1-phenylbutane
Chemical name	butylbenzene
CAS number	104-51-8
Structural formula	
Molecular formula	$C_{10}H_{14}$
Molar mass	134.22 g/mol
Melting point	–87.9 °C (NLM 2016)
Boiling point at 1013 hPa	183.3 °C (NLM 2016)
Density at 20 °C	0.8601 g/cm³ (NCBI 2016)
Vapour pressure at 25 °C	1.41 hPa (NLM 2016)
log K_{OW}	4.38 (NLM 2016)
Solubility at 25 °C	11.8 mg/l water (NLM 2016)
1 ml/m³ (ppm) ≙ 5.569 mg/m³	**1 mg/m³ ≙ 0.18 ml/m³ (ppm)**

The substance is used in the production of liquid crystals (METI 2002).

1 Toxic Effects and Mode of Action

n-Butylbenzene is oxidized at the side chain to alcohols and ketones; with exposure in vivo, the activities of various xenobiotic-metabolizing enzymes are thereby increased. The substance is irritating to the skin of rabbits. In a 2-generation study in rats, in addition to the deposition of hyaline droplets in the renal tubular epithelium, *n*-butylbenzene caused increased kidney weights and hepatocellular hypertrophy in the F0 generation at 300 mg/kg body weight and day. The RD_{50} in the mouse was found to be 710 ml/m³. Studies of eye irritation, sensitization, genotoxicity, developmental toxicity and carcinogenicity are not available.

2 Mechanism of Action

In vitro, *n*-butylbenzene caused the formation of reactive oxygen species in cerebellar granular cells of rats at concentrations of 313 µM and above. The activity increased in the order benzene < toluene < xylene < trimethylbenzene < *n*-butylbenzene (Dreiem et al. 2002). In these cells, *n*-butylbenzene was cytotoxic and the morphology of the cells exhibited elements of apoptosis and necrosis (Dreiem et al. 2005).

n-Butylbenzene caused the formation of reactive oxygen species in human neutrophil granulocytes in vitro at concentrations of 200 µM and above; benzene and xylene concentrations of up to 800 µM had no effect (Dreiem et al. 2003).

However, in rats given single intraperitoneal injections of *n*-butylbenzene of 1600 mg/kg body weight, the increased formation of hydroxyl radicals in the brain was not observed. Free malondialdehyde, as a marker of lipid peroxidation, decreased slightly in the brain within up to 4 hours after administration. Likewise, no increase in malondialdehyde was observed in the brain of rats exposed to *n*-butylbenzene concentrations of 830 ml/m^3 (vapour saturation concentration) 6 hours daily for 10 days. The observations made in vitro (see above) could therefore not be confirmed in vivo (Chalansonnet et al. 2013).

For *n*-butylbenzene, toluene, styrene, ethylbenzene and alpha-methylstyrene at a concentration of 3 mM, the uncoupling of oxidative phosphorylation was demonstrated, which was attributed to the stimulation of the passive influx of protons into the liver mitochondria of the rat (Mickiewicz and Rzeczycki 1988).

n-Butylbenzene did not bind to the oestrogen receptor of rats and humans up to a concentration of 0.1 mM and did not induce the activation of oestrogen receptor-mediated gene transcription in two assays with transfected yeast and HeLa cells (METI 2002).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Rabbits given an oral *n*-butylbenzene dose of 3 mmol/kg body weight (403 mg/kg body weight) excreted approximately 75% of the dose with the urine in the form of metabolites within 24 hours (see Section 3.2; El Masry et al. 1956).

In analogy to diethylbenzene, oral absorption of *n*-butylbenzene is assumed to be 90% of the dose (Hartwig and MAK Commission 2019). As there are no data for the uptake by inhalation of diethylbenzenes, the absorption of *n*-butylbenzene after inhalation exposure is assumed to be 60%, like that for ethylbenzene (Hartwig 2014).

There are no studies of dermal absorption available. With the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) fluxes of 337, 4.2 and 1.2 µg/cm^2 and hour, respectively, are calculated for a saturated aqueous solution. Assuming the exposure of 2000 cm^2 of skin for 1 hour, this would correspond to absorbed amounts of 674, 8.4 and 2.4 mg, respectively.

3.2 Metabolism

Daily intraperitoneal *n*-butylbenzene doses of 5 mmol/kg body weight (671 mg/kg body weight) on 4 consecutive days induced metabolic activity against aminopyrine and 7-ethoxycoumarin in the liver microsomes of rats. In addition, the hydroxylation of testosterone 2β, 6β, 7α and 16β was induced. The activity of the cytochrome P450 (CYP) enzymes CYP2A1, CYP2B1, CYP2B2, CYP2C6, CYP2E1 and CYP3A2 was increased. In a comparison with benzene, toluene, ethylbenzene and propylbenzene, it was found that the induction of CYP2B1 and CYP2B2 increased with the chain length on the aromatic ring. In rat liver microsomes in vitro, the activity of testosterone 2α, 2β, 6β, 16α and 16β hydroxylation was inhibited by *n*-butylbenzene. Here too, inhibition increased with the chain length of the alkyl residue. This shows that *n*-butylbenzene is a CYP inducer and is itself a ligand for CYP and that the binding to CYP correlates with the ability to induce CYP (Imaoka and Funae 1991).

Rat liver S9 mix was used to oxidize *n*-butylbenzene at positions 1 and 3 of the butyl residue to form monoalcohols, diols and ketones and the hydroxyketone. The main metabolite was 1-phenyl-1-butanone. The formation of the diols was enhanced by pretreatment of the rats with phenobarbital and β-naphthoflavone and inhibited with the CYP inhibitors SKF-525A and carbon monoxide, suggesting that CYP is involved in the oxidation (Takeshita et al. 1995).

Rabbits given an oral dose of *n*-butylbenzene of 3 mmol/kg body weight (403 mg/kg body weight) likewise oxidized *n*-butylbenzene at positions 1 and 3 of the butyl residue to form alcohols (42%–60% of the dose, excreted in the form of glucuronides) and phenylacetylglycine (15%–25%), which was presumably formed via oxidation to phenylbutyric acid and from 3-hydroxybutylbenzene; 2% of the dose was found in the form of hippuric acid. Ring hydroxylation resulting in *p*-hydroxyphenylacetic acid was supposed, as its urinary excretion was increased compared with the amount normally excreted endogenously (El Masry et al. 1956).

4 Effects in Humans

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The RD_{50} for irritation of the upper respiratory tract in mice after exposure for 30 minutes was 710 ml/m^3. From the data presented as a graph, an RD_{10} of 100 ml/m^3 can be estimated. Pulmonary irritation was not observed. From the RD_{50}, a threshold limit value for local irritation of 20 ml/m^3 was estimated (Nielsen and Alarie 1982).

5.1.2 Oral administration

There are no data available.

5.1.3 Dermal application

There are no data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

In Sprague Dawley rats given gavage doses of *n*-butylbenzene of 8.47 mmol/kg body weight and day (1137 mg/kg body weight and day) on 5 days per week for 2 weeks, no ototoxicity (loss of hair cells in the organ of Corti of the inner ear) was found, unlike with toluene, *p*-xylene, ethylbenzene and propylbenzene at the same dose level (Gagnaire and Langlais 2005).

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

An amount of 0.5 ml *n*-butylbenzene was applied on a gauze patch in a teflon chamber to the skin of 6 rabbits for 4 hours. Erythema with a score > 2 according to the Draize classification scheme was induced within 24 to 72 hours after the end of exposure. A 50% dilution was not irritating to the skin (Jacobs and Martens 1987).

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In an uterotrophic assay, *n*-butylbenzene was injected subcutaneously into 19-day-old rats at doses of 0, 40, 200, 1000 or 2000 mg/kg body weight and day on 3 consecutive days. Uterine weights were not increased compared with those in the controls. In a Hershberger assay, 56-day-old castrated and intact rats were given oral doses of 0, 200 or 600 mg/kg body weight and day on 10 days. The weights of the accessory reproductive organs were not changed compared with those in the controls. *n*-Butylbenzene was not found to have endocrine-disrupting properties in these tests (Yamasaki et al. 2002).

In a 2-generation study, groups of 24 male and 24 female Crj:CD(SD)IGS rats were given gavage doses of *n*-butylbenzene of 0, 30, 100 or 300 mg/kg body weight and day in 5 ml olive oil. The male F0 animals were 5 weeks old at the start of treatment and were treated for a total of 16 weeks, including 10 weeks before mating. The 5-week-old female F0 animals were treated in the same way up to day 21 after giving birth, for a maximum of 16 weeks. The F1 males were treated for 10 weeks prior to mating, starting at 3 weeks of age, and then for another 8 weeks. The female F1 animals were dosed from the age of 3 weeks, 10 to 12 weeks before mating and another 9 weeks until day 21 after giving birth. Food consumption, body weight gains, clinical signs of toxicity, fertility parameters, the time of preputial separation and vaginal opening, sperm parameters, follicle stimulating hormone, luteinizing hormone, testosterone, oestradiol, anogenital distance, sex ratio, number of births, viability, number of pups weaned, developmental milestones, reflexes, and organ weights were investigated. The pituitary gland, thyroid, parathyroid, liver, kidneys, adrenal glands, and primary and accessory reproductive organs were examined histopathologically.

At dose levels of 30 mg/kg body weight and day and above, the absolute and relative liver weights in the female F0 animals were increased in a dose-dependent manner by 10% to 15%. The authors attributed this to enzyme induction. A liver weight increase in this range is not considered by the Commission to be an adverse effect.

At 100 and 300 mg/kg body weight and day, salivation occurred after dosing in the F0 and F1 parent animals, and the oestrous cycle in the F0 animals was prolonged (not significant at 300 mg/kg body weight and day). The absolute and relative liver weights of the male F0 animals were increased in a dose-dependent manner by 7% to 20%, the relative kidney weights of the male F1 parent animals by 7 to 21% (control group: 0.56%, 100 mg/kg: 0.6%, 300 mg/kg 0.68%), with simultaneous detection of hyaline droplets in the renal tubular epithelium. A liver weight increase in this range is not considered by the Commission to be an adverse effect.

At 300 mg/kg body weight and day, body weight gains during lactation were reduced in the F0 and F1 parents. The number of implantations in the dams of the F0 generation, but not in those of the F1 generation, were reduced, consequently also the litter size was lower. The authors evaluated the reduced number of implantations in the F0 dams as an incidental finding, as this affected only two litters in which only 2 or 3 implantation sites were detected. The

historical control incidence for this is 0.86%. Furthermore, this finding did not occur in the F1 animals and also not at 1000 mg/kg body weight and day in the range-finding study. The histopathological examination, the hormone and sperm tests provided no evidence of an exposure-related cause. The absolute and relative liver weights in the F1 parent animals were increased by 11% to 17%. The relative and in some cases also the absolute kidney weights in the F0 and F1 parent animals were increased by up to 21%. In the female F1 parent animals, the absolute and the relative adrenal weights were increased. In male F0 and F1 parent animals, centrilobular hypertrophy of the liver occurred. Hyaline droplets were observed in the renal tubular epithelium in the male F0 parents and basophilic renal tubules occurred in the F0 and F1 animals. In the F1 and F2 offspring, the absolute and relative thymus weights were increased. The prolonged oestrous cycle was within the range of the historical control values (4–5 days) and this effect was not observed in the range-finding study at 1000 mg/kg body weight and day. The NOAEL (no observed adverse effect level) for adverse effects on fertility was thus 300 mg/kg body weight and day. The NOAEL for systemic toxicity was 30 mg/kg body weight and day, because at 100 mg/kg body weight and day the relative kidney weights of the male F1 parent animals were increased. Although the authors discussed that this might be due to the deposition of α-2u protein, as no hyaline droplets were found in the female F0 and F1 parents, they pointed out that the kidney weights were also increased in females at 300 mg/kg body weight and day (Izumi et al. 2005). The increased kidney weights in male F1 parents cannot be used for the derivation of an occupational exposure limit value due to the continuous exposure from conception onwards. The kidney weights of the F0 animals were not increased at 100 mg/kg body weight and day, and no centrilobular hypertrophy of the liver was observed. Therefore, this dose is the NOAEL for systemic toxicity. The US EPA likewise considered 100 mg/kg body weight and day to be the NOAEL of the study, because the deposition of hyaline droplets in the kidneys at this dose was observed only in the F1 generation and not in the females. The critical effect was hepatocellular hypertrophy at 300 mg/kg body weight and day. The effect on the thymus weights of the offspring was considered questionable, since the absolute and relative weights were not changed together and were proportional to body weight changes (US EPA 2010).

In a description of 2-generation studies with additional parameters to investigate possible endocrine effects, also the study by Izumi et al. (2005) is included; the review came to the conclusion that *n*-butylbenzene does not have endocrine effects (Yamasaki et al. 2005).

5.5.2 Developmental toxicity

There are no data available.

In the 2-generation study described above (Section 5.5.1), no effects on the offspring occurred, with the exception that at 300 mg/kg body weight and day the thymus weights of the F1 and F2 offspring were increased. Therefore, a NOAEL for postnatal developmental toxicity of 100 mg/kg body weight and day was given by the authors (Izumi et al. 2005). The effect on the thymus weights of the offspring was considered questionable because the absolute and relative weights were not changed together and were proportional to body weight changes (US EPA 2010). The increased kidney weights in the male F1 parents at 100 mg/kg body weight and day and above are not necessarily indicative of postnatal developmental toxicity, since increased kidney weights were observed also in the F0 generation; it is therefore a general, directly systemically toxic effect. In the F0 generation, significantly increased kidney weights occurred only at 300 mg/kg body weight and day (Izumi et al. 2005). Thus, the F1 parents were more sensitive, possibly because of the longer exposure period (in utero, during lactation and from the 3rd week of life), which is not relevant to the workplace, compared with the F0 animals (only from the 5th week of life). The NOAEL for foetotoxicity and postnatal developmental toxicity is therefore 300 mg/kg body weight and day. There was no examination of visceral and skeletal malformations.

5.6 Genotoxicity

5.6.1 In vitro

There are no data available.

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value/classification)

Critical effects are the increased kidney weights and centrilobular hypertrophy of hepatocytes observed in a 2-generation study in rats at 300 mg/kg body weight and day.

MAK value. In a 2-generation study, the kidney weights were increased in the male F1 parents at 100 mg/kg body weight and day and above, and in the females at 300 mg/kg body weight and day. The kidney weights were significantly increased in the F0 generation only at 300 mg/kg body weight and day. Thus, the male F1 animals were more sensitive, possibly due to the longer exposure period (in utero, during lactation and from the 3rd week of life), compared with the F0 animals, who were exposed only from the 5th week of life. As the exposure of the F1 animals does not correspond to that at the workplace, the NOAEL for the F1 animals was not used to derive the MAK value. The corresponding NOAEL for the F0 animals is 100 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL 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 value for the rat (1:4), the oral absorption of 90% (Section 3.1), the body weight (70 kg) and respiratory volume (10 m^3) of the person and the 60% absorption by inhalation (Section 3.1). The concentration calculated from this is 368 mg/m^3 (66 ml/m^3). No data are available for a possible increase in the effects in the case of long-term exposure; this is therefore assumed (1:2). Taking into consideration that the data are extrapolated from experimental studies with animals to humans (1:2) and using the Preferred Value Approach, a MAK value of 10 ml/m^3 is obtained.

In a 13-week study in rats, a diethylbenzene isomer mixture was found to have no irritant effects on the respiratory tract up to the highest concentration tested of 258 ml/m^3 (Hartwig and MAK Commission 2019). The MAK value of 10 ml/m^3 is lower than that of all other alkylbenzenes evaluated by the Commission for which human data for irritation are available (ethylbenzene, styrene, trimethylbenzenes). An irritant effect is therefore not to be expected at 10 ml *n*-butylbenzene/m^3. Another supporting factor is that the RD_{50} of 710 ml *n*-butylbenzene/m^3 results in a threshold limit value of 20 ml/m^3 for sensory irritation.

Peak limitation. Because of the systemic effects, *n*-butylbenzene has been assigned to Peak Limitation Category II with the default excursion factor of 2, as no data for the half-life of the substance are available. In view of the permitted short-term concentrations of other alkylbenzenes and the RD_{50} (see above), an irritant effect is not expected at the permitted short-term concentration of 20 ml/m^3 for *n*-butylbenzene.

Prenatal toxicity. In a 2-generation study, no effects on the offspring regarding body weight development, litter parameters, the start of puberty, developmental milestones and reflexes were found. The increase in the thymus weights in the F1 and F2 offspring at 300 mg/kg body weight (Izumi et al. 2005) was considered questionable, since the absolute and relative weights were not changed together and were proportional to body weight changes (US EPA 2010). The increased kidney weights in the male F1 parents at 100 mg/kg body weight and above are not necessarily indicative of postnatal developmental toxicity, since increased kidney weights occurred also in the F0 generation; it is therefore a general, directly systemically toxic effect. The NOAEL for foetotoxicity and postnatal developmental toxicity is 300 mg/kg body weight and day. As no study of visceral and skeletal malformations has been carried out, *n*-butylbenzene has been assigned to Pregnancy Risk Group D.

Germ cell mutagenicity and carcinogenicity. No data are available and, considering the structure of the substance, mutagenicity is not to be suspected. Therefore, there is no corresponding classification.

Absorption through the skin. In the absence of in vitro and in vivo data, the assessment of dermal absorption is based on mathematical models. The model of Fiserova-Bergerova et al. (1990) shows a better agreement with the in vivo data for other alkyl aromatics investigated and is therefore used for this group of substances. According to this model (Section 3.1), the exposure of 2000 cm^2 of skin for 1 hour to a saturated aqueous solution leads to the dermal absorption of a maximum amount of 674 mg.

The NOAEL for systemic effects after oral administration from the 2-generation study in rats is 100 mg/kg body weight and day in the F0 generation (see above). For the extrapolation of this dose as the systemic NOAEL to humans the following toxicokinetic data are taken into consideration: the species-specific correction value (1:4) for the rat, the assumed oral absorption of 90% (see above), the daily exposure of the animals in comparison with the 5 days exposure at the workplace (7:5), the body weight (70 kg) of the person, a possible increase in the effects over time (1:2) and the extrapolation of the data from animal experiments to humans (1:2). This results in a systemically tolerable dose of 551 mg.

This means that the amount absorbed through the skin calculated using the Fiserova-Bergerova model is more than 25% of the systemically tolerable dose, and *n*-butylbenzene has been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data available. *n*-Butylbenzene is therefore not designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

References

Chalansonnet M, Carabin N, Boucard S, Cosnier F, Nunge H, Gagnaire F (2013) Study of the potential oxidative stress induced by six solvents in the rat brain. Neurotoxicology 35: 71–83. https://doi.org/10.1016/j.neuro.2012.12.002

Dreiem A, Myhre O, Fonnum F (2002) Relationship between lipophilicity of C6–10 hydrocarbon solvents and their ROS-inducing potency in rat cerebellar granule cells. Neurotoxicology 23(6): 701–709. https://doi.org/10.1016/S0161-813X(02)00010-4

Dreiem A, Myhre O, Fonnum F (2003) Involvement of the extracellular signal regulated kinase pathway in hydrocarbon-induced reactive oxygen species formation in human neutrophil granulocytes. Toxicol Appl Pharmacol 190(2): 102–110. https://doi.org/10.1016/s0041-008x(03)00158-3

Dreiem A, Ring A, Fonnum F (2005) Organic solvent-induced cell death in rat cerebellar granule cells: structure dependence of C10 hydrocarbons and relationship to reactive oxygen species formation. Neurotoxicology 26(3): 321–330. https://doi.org/10.1016/j.neuro.2005.01.006

El Masry AM, Smith JN, Williams RT (1956) Studies in detoxication. 69. The metabolism of alkylbenzenes: n-propylbenzene and n-butylbenzene with further observations on ethylbenzene. Biochem J 64(1): 50–56. https://doi.org/10.1042/bj0640050

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17(5): 617–635. https://doi.org/10.1002/ajim.4700170507

Gagnaire F, Langlais C (2005) Relative ototoxicity of 21 aromatic solvents. Arch Toxicol 79(6): 346–354. https://doi.org/10.1007/s00204-004-0636-2

Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. Am J Ind Med 23(5): 711–719. https://doi.org/10.1002/ajim.4700230505

Hartwig A, editor (2014) Ethylbenzene. MAK Value Documentation, 2012. In: The MAK-Collection for Occupational Health and Safety. Part I: MAK Value Documentations. Weinheim: Wiley-VCH. https://doi.org/10.1002/3527600418.mb10041e5214

Hartwig A, MAK Commission (2019) Diethylbenzene (all isomers). MAK Value Documentation, 2018. MAK Collect Occup Health Saf 4(3): 1100–1129. https://doi.org/10.1002/3527600418.mb13501isme6519

Imaoka S, Funae Y (1991) Induction of cytochrome P450 isozymes in rat liver by methyl n-alkyl ketones and n-alkylbenzenes. Effects of hydrophobicity of inducers on inducibility of cytochrome P450. Biochem Pharmacol 42 Suppl: S143-150. https://doi.org/10.1016/0006-2952(91)90404-s

Izumi H, Kimura E, Ota T, Shimazu S (2005) A two-generation reproductive toxicity study of n-butylbenzene in rats. J Toxicol Sci 30 Spec No.: 21–38. https://doi.org/10.2131/jts.30.s21

Jacobs G, Martens M (1987) Evaluation of the test method for skin irritation as prescribed by OECD and EEC. J Toxicol Cutaneous Ocul Toxicol 6(3): 215–225. https://doi.org/10.3109/15569528709051528

METI (Ministry of Economy Trade and Industry of Japan) (2002) Hazard assessment of n-butylbenzene. Tokyo: METI. http://www.meti.go.jp/english/report/downloadfiles/gED0303e.pdf, accessed 21 Apr 2016

Mickiewicz W, Rzeczycki W (1988) Effect of styrene and other alkyl benzene derivatives on oxidation of FAD- and NAD-linked substrates in rat liver mitochondria. Biochem Pharmacol 37(23): 4439–4444. https://doi.org/10.1016/0006-2952(88)90658-2

NCBI (National Center for Biotechnology Information) (2016) n-Butylbenzene. PubChem annotation record. Source: HSDB. https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7211, accessed 16 Jun 2016

Nielsen GD, Alarie Y (1982) Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties. Toxicol Appl Pharmacol 65(3): 459–477. https://doi.org/10.1016/0041-008x(82)90391-x

NLM (National Library of Medicine) (2016) n-Butylbenzene. ChemIDplus Data Bank. https://chem.nlm.nih.gov/chemidplus/rn/104-51-8, accessed 16 Jun 2016

Takeshita M, Miura M, Unuma Y, Iwai S, Sato I, Arai T, Kosaka K (1995) Regio- and stereo-selective oxidation of phenylbutane by rat liver. Res Commun Mol Pathol Pharmacol 89(3): 351–356

US EPA (US Environmental Protection Agency) (2010) Provisional peer-reviewed toxicity values for n-butylbenzene. FINAL 9-13-2010. Washington, DC: US EPA. https://hhpprtv.ornl.gov/issue_papers/Butylbenzenen.pdf, accessed 12 Apr 2016

Wilschut A, ten Berge WF, Robinson PJ, McKone TE (1995) Estimating skin permeation. The validation of five mathematical skin permeation models. Chemosphere 30(7): 1275–1296. https://doi.org/10.1016/0045-6535(95)00023-2

Yamasaki K, Sawaki M, Noda S, Takatsuki M (2002) Uterotrophic and Hershberger assays for n-butylbenzene in rats. Arch Toxicol 75(11–12): 703–706. https://doi.org/10.1007/s00204-001-0296-4

Yamasaki K, Takahashi M, Yasuda M (2005) Two-generation reproductive toxicity studies in rats with extra parameters for detecting endocrine disrupting activity: introductory overview of results for nine chemicals. J Toxicol Sci 30 Spec No.: 1–4. https://doi.org/10.2131/jts.30.s1