The MAK Collection for Occupational Health and Safety

Diisotridecyl phthalate, ditridecyl phthalate

MAK Value Documentation – Translation of the German version from 2019

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Keywords: diisotridecyl phthalate; ditridecyl phthalate; toxicity; carcinogenicity; metal-working fluids

Citation Note: Hartwig A, MAK Commission. Diisotridecyl phthalate, ditridecyl phthalate. MAK Value Documentation – Translation of the German version from 2019. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2019 Nov;4(4):1989-2002]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2025. https://doi.org/10.34865/mb11906kske6619_w

Republished (online): 08 Aug 2025

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb11906kske6619

Addendum completed: 21 Mar 2018

Published (online): 13 Nov 2019

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

Diisotridecyl phthalate, ditridecyl phthalate / Bis(11-methyldodecyl) benzene-1,2-dicarboxylate, ditridecyl benzene-1,2-dicarboxylate

MAK value documentation

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DOI: 10.1002/3527600418.mb11906kske6619

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated diisotridecyl phthalate (a mixture of various isomers) [27253-26-5] and ditridecyl phthalate [119-06-2] considering all toxicological endpoints. Available publications and unpublished study reports are described in detail. The critical effect is centrilobular hepatocyte hypertrophy following prolonged oral exposure of rats. There are signs of peroxisome proliferating activity which has also been observed with other phthalates like di(2-ethylhexyl) phthalate. Diisotridecyl phthalate and ditridecyl phthalate are not genotoxic. No carcinogenicity study has been performed, but due to the similarity to di(2-ethylhexyl) phthalate, liver carcinogenicity cannot be excluded. Therefore, diisotridecyl phthalate and ditridecyl phthalate are classified in Category 3B for suspected carcinogens.

Both phthalates cause at most minimal irritation to the eyes and skin of rabbits. As no inhalation study has been performed, possible long-term effects on larynx and nasal goblet cells, the targets of other phthalates, cannot be evaluated. Therefore, no maximum concentration at the workplace (MAK value) can be derived.

Ditridecyl phthalate does not cause developmental toxicity in rats up to an oral dose of 100 mg/kg body weight and day, the highest dose tested. Skin contact is not expected to contribute significantly to systemic toxicity. Limited data show no sensitization.

Keywords

diisotridecyl phthalate; ditridecyl phthalate; bis(isotridecyl)phthalate; phthalic acid diisotridecyl ester; ditridecylbenzene-1,2-dicarboxylate; phthalic acid ditridecyl ester; 1,2-benzenedicarboxylic acid diisotridecyl ester; 1,2-benzenedicarboxylic acid ditridecyl ester; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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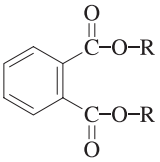
1990

Diisotridecyl phthalate, ditridecyl phthalate

MAK value	**not yet established, see List of MAK and BAT Values, Section II b**
Peak limitation	**–**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity (2018)	**Category 3B**
Prenatal toxicity	**–**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	**diisotridecyl phthalate**: bis(isotridecyl)phthalate phthalic acid diisotridecyl ester **ditridecyl phthalate**: ditridecylbenzene-1,2-dicarboxylate phthalic acid ditridecyl ester
CAS number and chemical name	**diisotridecyl phthalate**: 27253-26-5: 1,2-benzenedicarboxylic acid diisotridecyl ester **ditridecyl phthalate**: 119-06-2: 1,2-benzenedicarboxylic acid ditridecyl ester

Molecular formula



diisotridecyl phthalate:

$R = C_{13}H_{27}$ (UVCB substance (Unknown or Variable composition, Complex reaction products or Biological materials))

ditridecyl phthalate:

$R = (CH_2)_{12}CH_3$

$C_{34}H_{58}O_4$

Molar mass

530.83 g/mol

Melting point

diisotridecyl phthalate:

−38 °C (ECB 2000); −41 °C (impurity: 0.593% bisphenol A) (ECHA 2017)

ditridecyl phthalate:

−37 °C (CPSC 2011)

Boiling point

diisotridecyl phthalate:

255–265 °C at 5 hPa, substance stabilized with about 0.5% bisphenol A (ECB 2000); 330 °C at 1021.5 hPa, substance stabilized with about 0.6% bisphenol A (ECHA 2017)

ditridecyl phthalate:

501 °C at 1013 hPa (CPSC 2011)

Density

diisotridecyl phthalate:

0.951–0.954 g/cm^3 at 20 °C, substance stabilized with about 0.5% bisphenol A (ECB 2000); 0.948 g/cm^3 at 20 °C, substance stabilized with about 0.6% bisphenol A (ECHA 2017)

ditridecyl phthalate:

0.9525 g/cm^3 at 25 °C (CPSC 2011)

Vapour pressure	**diisotridecyl phthalate**:
	< 0.01 hPa at 20 °C, substance stabilized with about 0.5% bisphenol A (ECB 2000); < 0.00001 hPa at 37.8 °C, substance stabilized with about 0.6% bisphenol A (ECHA 2017)
	ditridecyl phthalate:
	2.5–3.6 × 10^{-10} hPa at 25 °C (CPSC 2011)
log K_{OW}[1)]	**diisotridecyl phthalate**:
	13.5 at 23 °C, substance stabilized with about 0.6% bisphenol A (ECHA 2017)
	ditridecyl phthalate:
	12.1 (CPSC 2011)
Solubility in water	**diisotridecyl phthalate**:
	4.4–13.1 mg/l at 20 °C, substance stabilized with about 0.5% bisphenol A (ECB 2000); < 1 mg/l at 23 °C, substance stabilized with about 0.6% bisphenol A (ECHA 2017)
	ditridecyl phthalate:
	1.48 × 10^{-9} mg/l at 25 °C (calculated; CPSC 2011); 7 × 10^{-8} mg/l (temperature not specified) (CPSC 2011)
Stability	no data
Production	**diisotridecyl phthalate**:
	esterification of phthalic acid with isotridecanol (UVCB)
	ditridecyl phthalate:
	esterification of phthalic acid with tridecanol (CPSC 2011)
Purity	**diisotridecyl phthalate**:
	99.1% (ECHA 2017)
	ditridecyl phthalate:
	> 99.5% (CPSC 2011)

1) octanol/water partition coefficient

Impurities	**diisotridecyl phthalate**: bisphenol A (ECHA 2017) **ditridecyl phthalate**: 0.1–0.3% w/w antioxidants such as 1,1,3-tris(2-methyl-4-hydroxy-5-tert-butylphenyl)butane; 0.5% ortho-isomer of bisphenol A (CPSC 2011)
Uses	**diisotridecyl phthalate**: in lubricants, glues, coatings, cables and the processing of polymers (ECHA 2017) **ditridecyl phthalate**: in PVC, metal-working fluids (10% to 30%), sealing liquids, cable and wire sheathing and insulation in the automobile and building industry (CPSC 2011)

Very few data are available for **diisotridecyl phthalate** [27253-26-5], which is included in the list of "Components of metal-working fluids, hydraulic fluids and other lubricants". Therefore, for purposes of the evaluation, this documentation draws upon the data for the structurally similar **ditridecyl phthalate** [119-06-2].

The documentation is based primarily on the IUCLID (ECB 2000) dataset and the dataset publicly available through REACH (ECHA 2017) for **diisotridecyl phthalate** and the evaluation of **ditridecyl phthalate** by the US Consumer Product Safety Commission (CPSC 2011).

Diisotridecyl phthalate is classified as a UVCB substance (Chemical Substances of Unknown or Variable Composition) in the REACH dataset (ECHA 2017).

1 Toxic Effects and Mode of Action

The acute toxicity of **diisotridecyl phthalate** and **ditridecyl phthalate** is low.

In a combined study of reproductive toxicity and repeated oral exposure of rats, **ditridecyl phthalate** induced centrilobular hepatocyte hypertrophy in female rats at doses of 50 mg/kg body weight and day and above and an increase in the absolute kidney weights and eosinophilic foci in the renal tubular cells in male rats at higher doses. There was evidence of peroxisome proliferation. Neither fertility parameters nor reproductive organs were impaired up to the highest dose tested of 250 mg/kg body weight and day. In a prenatal developmental toxicity study in rats, neither developmental nor maternal toxicity was observed up to the highest **ditridecyl phthalate** dose of 1000 mg/kg body weight and day.

Both phthalates induced only minimal irritation of the skin and eyes of rabbits.

The studies available in humans and guinea pigs provide no evidence of sensitizing effects on the skin induced by **diisotridecyl phthalate**. There are no studies of these effects after exposure to **ditridecyl phthalate**.

Neither **diisotridecyl phthalate** nor **ditridecyl phthalate** was mutagenic in bacteria. A test for chromosomal aberrations in mammalian cells yielded negative results, but is difficult to interpret because of precipitation of the test substance. In a micro-

nucleus test with intraperitoneal injection of **diisotridecyl phthalate** in mice, no clastogenic effects were observed. There are no studies of carcinogenicity.

2 Mechanism of Action

Peroxisome proliferation

In a combined study of reproductive toxicity and repeated oral exposure of rats to **ditridecyl phthalate** (see Section 5.2.2), a slight increase in relative liver weights of +17% and +15% was observed in male and female rats, respectively, at the dose of 250 mg/kg body weight and day. The catalase activity was determined in 2 male animals of each dose group by means of catalase-positive granules in the liver; this activity was slightly increased only in the high dose group (CPSC 2011) and is evidence of peroxisome proliferation (Maronpot et al. 2010). A lack of detailed data and the very small number of animals make it difficult to evaluate the findings.

Oestrogenic effects

Ditridecyl phthalate did not induce oestrogenic effects either in vitro in recombinant yeast cells with human oestrogen receptors, or in proliferation assays with the human cell lines MCF-7 or ZR-75. Changes in the oestrus cycle were not observed in female Sprague Dawley rats given oral doses of up to 250 mg/kg body weight and day for 14 days (see Section 5.2.2 and 5.5.; CPSC 2011).

3 Toxicokinetics and Metabolism

There are no studies available for diisotridecyl phthalate and ditridecyl phthalate.

Rats absorbed 73% of the structurally similar **diisodecyl phthalate** by inhalation (documentation "Diisodecyl phthalate, mixture of isomers" 2011). This percentage is assumed also for the absorption of diisotridecyl phthalate and ditridecyl phthalate.

After oral exposure of rats to **diisodecyl phthalate** doses of 0.1, 11.2 and 1000 mg/kg body weight, 41%, 32% and 13%, respectively, was excreted with the urine. The percentage excreted with the faeces was 58%, 66% and 82%, respectively; at the low dose, 70% of the amount excreted was in the form of metabolites, at the high dose, this fraction was 40% (ECHA 2017). Therefore, at a dose of 10 mg/kg body weight, about 55% of 66% = 36% would be excreted in metabolite form. Together with the urinary excretion of 32%, the mean oral absorption is calculated to be 68%. This is assumed also for diisotridecyl phthalate and ditridecyl phthalate.

With respect to absorption through the skin, a study of the structurally similar **diisononyl phthalate** is available. An amount of 0.1 or 0.2 ml (about 1.2 ml/kg body weight) of diisononyl phthalate was applied once to the shaved skin of the back of rats and the application site was occluded. After 7 days, 3% of the low dose and 4% of the high dose had been absorbed. Absorption of 1.5×10^{-5} mg/cm^2 and hour was calculated for the low dose (ECHA 2017). Assuming the same density of 0.95 g/cm^3 as for **diisotridecyl phthalate**, a flux of 0.0014 mg/cm^2 and hour is calculated. This flux value is assumed also for **diisotridecyl phthalate** and **ditridecyl phthalate**.

Thus, under standard conditions (2000 cm^2 of skin, 1-hour exposure), 2.8 mg of diisotridecyl phthalate and ditridecyl phthalate are absorbed.

In a similar study, epicutaneous absorption of **diisodecyl phthalate** in rats after occlusive application was investigated. Only 0.04% of the substance was excreted with the urine and faeces after 24 hours and 0.5% after 7 days; about 1% was found in the tissues after 7 days (Elsisi et al. 1989).

On the basis of an in vivo study in rats, an absorption rate of 1.3 µg/cm^2 and hour was calculated for the structurally similar **diisodecyl phthalate**. Thus, under standard conditions, absorption would be 2.7 mg after 1-hour exposure of 2000 cm^2 of skin. The amount absorbed through human skin is probably considerably less than the amount absorbed through rat skin, as has been described in the evaluation of the structurally similar diisodecyl phthalate (documentation "Diisodecyl phthalate, mixture of isomers" 2011).

As the log K_{OW} is greater than 6 and thus outside of the scope of validity for the mathematical models, the dermal absorption of the two substances cannot be calculated.

4 Effects in Humans

Data are available only for sensitizing effects on the skin.

Sensitization was not induced in 104 volunteers in a repeated insult patch test (RIPT) with 24-hour occlusive application of undiluted **diisotridecyl phthalate** 3 times a week for 3 weeks. At the challenge treatment 14 days after the last induction treatment, no reactions were induced by the undiluted substance that were evaluated as irritant or allergic. The authors reported that of the initial number of 128 volunteers included in the study, 24 left the study early for reasons unrelated to treatment (no other details) (Medeiros et al. 1999).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available.

5.1.2 Oral administration

A limit test carried out in 1984 according to OECD Test Guideline 401 with exposure of 5 male and 5 female Wistar rats to **diisotridecyl phthalate** (stabilized with 0.5% bisphenol A) determined a LD_{50} value greater than 10 000 mg/kg body weight. The animals were followed up for 14 days. No mortality was reported (ECB 2000; ECHA 2017).

An oral **ditridecyl phthalate** dose (purity 93.7%–100%) of 2000 mg/kg body weight did not lead to either substance-induced effects or mortality in 5 male and 5 female Sprague Dawley rats within the 14-day observation period (CPSC 2011).

5.1.3 Dermal application

In a study carried out in the 1960s, a dermal LD_{50} value that was greater than 20 ml/kg body weight (> 19 000 mg/kg body weight at a density of 0.95 g/cm^3) was determined for **ditridecyl phthalate** in male New Zealand White rabbits. The test substance was applied occlusively to the shaved skin of 4 animals for 24 hours. The observation period lasted 14 days. Skin reactions were not reported (CPSC 2011).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

In a combined study of toxicity after repeated exposure and of reproductive and developmental toxicity (screening study available in the form of a Japanese study report and an English abstract), rats were given daily gavage doses of **ditridecyl phthalate** of 0, 10, 50 or 250 mg/kg body weight and day. Exposure of the females began 15 days before mating, continued during gestation and lasted up to day 4 of lactation. The males were exposed for 6 weeks.

Mortality was not reported up to the high dose. Salivation was observed in the males of the high dose group in weeks 3 and 5 (in 1 of 13 animals at each time point) and in week 6 (7 of 13 animals), and in week 6 in 2 of 13 males of the group exposed to 50 mg/kg body weight and day. In the females, body weight gains were significantly decreased in comparison with those in the control animals at 50 mg/kg body weight and day and above 15 days before mating, which led to a significant decrease in body weights (–5%) in the high dose group at the end of this period. At the end of the overall study, the body weights were significantly lower than those of the control animals also in the group exposed to 50 mg/kg body weight and day. No effects on body weights and body weight gains were observed in the males over the entire study period. Effects on feed consumption were not found in either the males or females. The results of the haematological examination were reported only for the males. The slight decreases in the mean corpuscular haemoglobin (–3.7%) and the mean corpuscular haemoglobin concentration (–1.5%) in the high dose group were statistically significant.

Effects on the liver were observed in animals of both sexes. Specifically, these were an increase in the relative, but not the absolute, liver weights of the males after exposure to 250 mg/kg body weight and day (+17%) and of the females at 50 (+10%) and 250 mg/kg body weight and day (+15%). Gross-pathological examination of the females, but not the males, revealed an enlarged liver in 2 of the 13 animals of the high dose group. Centrilobular hepatocyte hypertrophy was found in males and females;

this finding was statistically significant in the males only at the dose of 250 mg/kg body weight and day while the incidence and severity were significantly increased in the females in a dose-dependent manner at doses of 50 mg/kg body weight and day and above. A significant decrease in the incidence and severity of periportal fatty deposits was observed in the males, but not in the females. Catalase-positive granules were determined in the livers of 2 males of each dose group; these were slightly increased only in the high dose group. Catalase activity was not investigated in the liver of the females. The alkaline phosphatase activity in the serum of males of the high dose group was significantly increased by 21% in comparison with that in the controls.

The absolute, but not the relative, kidney weights were significantly increased in the males of the high dose group. The gross-pathological examination revealed enlarged kidneys in 3 of the 13 animals. The histopathological examination of this dose group found an increase in the incidence and severity of eosinophilic foci in the renal tubular cells (regeneration foci). None of these findings were reported for the females. In the females, slight hyperplasia of the renal pelvis epithelium was observed in only 1 animal of the high dose group. Very slight hyperplasia of the urothelium was found in the bladder of 2 of the 13 female animals of the high dose group.

The LOAEL (lowest observed adverse effect level) of this study was 50 mg/kg body weight and day and was based on an increase in the number of females with centrilobular hepatocyte hypertrophy. The NOAEL (no observed adverse effect level) was 10 mg/kg body weight and day. The same findings were determined in the liver of the males; however, the males were slightly less sensitive. In addition, in the 15 days before mating, body weight gains were significantly decreased in the females in comparison with those in the controls at doses of 50 mg/kg body weight and day and above (CPSC 2011).

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study carried out in 1984 according to OECD Test Guideline 404, **diisotridecyl phthalate** (stabilized with 0.5% bisphenol A) did not cause irritation of the skin after 4-hour semi-occlusive application of 0.5 ml of the test substance to the skin of 6 Small White Russian rabbits. The substance was washed off with warm water after 4 hours. The observation period lasted 9 days. After 24, 48 and 72 hours, the primary irritation index was 0.34 of a maximum of 8.0. Erythema was found in 1 animal, oedema in another. All findings were fully reversible within the observation period (ECB 2000; ECHA 2017).

A study from the 1960s reported a primary skin irritation index for **ditridecyl phthalate** of 2 of a maximum of 10 after 0.01 ml of the test substance was applied uncovered to the skin of 5 albino rabbits and the animals were observed for 24 hours (CPSC 2011).

5.3.2 Eyes

In a study carried out in 1984 according to OECD Test Guideline 405 with 6 Small White Russian rabbits, irritation of the eyes was not induced by the instillation of 0.1 ml of **diisotridecyl phthalate** (stabilized with 0.5% bisphenol A). The eyes were not rinsed. The observation period lasted 21 days. After 24, 48 and 72 hours, the primary irritation index was 2.17 of a maximum of 110. The individual values were 0 of a maximum of 4 for the cornea, 0 of a maximum of 2 for the iris, 0.11 of a maximum of 3 for redness of the conjunctivae and 0 of a maximum of 4 for swelling of the conjunctivae. The findings were completely reversible within 48 hours (ECB 2000; ECHA 2017).

In a study from the 1960s, a primary ocular irritation index of 2 of a maximum of 10 was reported for **ditridecyl phthalate** after 0.5 ml of the undiluted test substance was instilled into the eyes of rabbits (no other details; CPSC 2011).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

Two Bühler tests carried out according to the test guidelines with undiluted **diisotridecyl phthalate** yielded negative results. In the tests, 19 and 20 guinea pigs were treated for induction with three 6-hour occlusive applications of diisotridecyl phthalate at a purity of 99.6% within a 3-week period. A reaction was not observed in any of the treated animals or in the 10 animals in each control group at the challenge treatment with undiluted diisotridecyl phthalate 2 weeks after the last induction treatment (ECHA 2017).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In the study discussed in Section 5.2.2. with exposure of rats to gavage doses of **ditridecyl phthalate**, no significant treatment-induced effects on the oestrus cycle, mating, fertility, the number of corpora lutea and implantations, gestation, and the number of offspring, the sex ratio, body weights, and survival of the offspring up to day 4 of lactation were observed up to the highest dose tested of 250 mg/kg body weight and day. The decrease in the live born index (number of living offspring on day 0/total number of offspring on day 0 × 100) observed in the 250 mg/kg group (87.7 ± 28.4 compared with 99.6 ± 1.6 in the controls) was statistically significant. However, the toxicological relevance of the finding is questionable as none of the individual values on which the calculation of the index was based differed significantly from the values of the control animals. Reduced lactation was reported for the high dose group, but no other details were provided. This had no effect on the weight

or viability of the offspring. Exposure to ditridecyl phthalate did not have an effect on the organ weights of the testes, epididymis or ovaries. No substance-induced histopathological findings were determined in these organs.

Therefore, the NOAEL for fertility in males was 250 mg/kg body weight and day and in females 50 mg/kg body weight and day on the basis of the reduced lactation observed in the animals of the high dose group (CPSC 2011).

5.5.2 Developmental toxicity

The study discussed in Section 5.2.2. and 5.5.1 found no significant treatment-induced effects on the number of offspring, the sex ratio, body weights, external malformations and survival of the offspring in rats treated with **ditridecyl phthalate** up to day 4 of lactation. The NOAEL for foetotoxicity was 250 mg/kg body weight and day, the highest dose tested (CPSC 2011). Visceral and skeletal malformations were not investigated.

In a developmental toxicity study, groups of 20 to 24 Sprague Dawley rats were given gavage doses of **ditridecyl phthalate** (purity > 98%) of 0, 250, 500 or 1000 mg/kg body weight and day from gestation days 6 to 20. No effects on maternal body weights or feed consumption were observed. The treatment did not have a significant effect on the number of living foetuses, post-implantation losses and resorptions, the sex ratio and foetal body weights. Toxic effects on development were not observed up to the highest dose of 1000 mg/kg body weight and day. There were no substance-induced effects on foetal anogenital distance (AGD). The NOAEL for developmental toxicity and maternal toxicity was 1000 mg/kg body weight and day, the highest dose tested (Saillenfait et al. 2013).

5.6 Genotoxicity

5.6.1 In vitro

In a study carried out in the 1970s, **diisotridecyl phthalate** was not found to be mutagenic in a mutagenicity test in the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of up to 5000 µg/plate both with and without the addition of a metabolic activation system (ECB 2000).

In two studies, **ditridecyl phthalate** did not induce mutations in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 uvrA both with and without the addition of a metabolic activation system. One study reported precipitation of the test substance (solvent: dimethyl sulfoxide) at concentrations above 625 µg/plate and cytotoxicity at the highest concentration of 5000 µg/plate. The second study reported neither precipitation of the test substance nor cytotoxicity up to 10 000 µg/plate. Concurrent positive and negative controls confirmed the functionality of the test systems (CPSC 2011).

Ditridecyl phthalate did not induce chromosomal aberrations in Chinese hamster lung cells. The study was carried out both with and without the addition of a metabolic activation system at concentrations of up to 4750 µg/ml. Precipitation of the test substance (solvent: dimethyl sulfoxide) was observed at all concentrations.

Concurrent positive and negative controls confirmed the functionality of the test system (CPSC 2011).

5.6.2 In vivo

In a valid micronucleus test carried out in mice in 1994, **diisotridecyl phthalate** (purity 99.5%; 0.5% bisphenol A) did not induce a significant increase in micronuclei in polychromatic erythrocytes of the bone marrow. In this study, 10 male and 10 female NMRI mice were given a single intraperitoneal injection of the test substance at a dose of 2000 mg/kg body weight and day. The samples were taken 24 and 48 hours after treatment. Neither clinical signs of toxicity nor cytotoxicity in the target cells was observed. The concurrent positive control confirmed the functionality of the test system (ECHA 2017).

5.7 Carcinogenicity

There are no studies available.

6 Manifesto (MAK value/classification)

The critical effect in rats after repeated oral administration is centrilobular hepatocyte hypertrophy accompanied by a slight increase in relative liver weights. There is evidence of peroxisome proliferation.

MAK value. There are no studies with inhalation exposure of humans or animals to **ditridecyl phthalate** or **diisotridecyl phthalate**. Like the other phthalates evaluated to date by the Commission, both phthalates induce at most slight irritation of the skin and eyes. Data on possible local effects on the respiratory tract such as those with di-*n*-butyl phthalate aerosol which induces metaplasia in the larynx and goblet cell hyperplasia (documentation "Di-*n*-butyl phthalate" 2013) are not available for **ditridecyl phthalate** and **diisotridecyl phthalate.**

In a combined study of reproductive toxicity and toxicity induced by repeated oral exposure of rats to **ditridecyl phthalate** (CPSC 2011), the LOAEL of 50 mg/kg body weight and day was derived on the basis of an increase in the number of females with centrilobular hepatocyte hypertrophy, reduced body weight gains in the 15 days before mating and lower body weights than the control animals at the end of the study. The NOAEL was 10 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of the 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 (68%), the body weight (70 kg) and respiratory volume (10 m^3) of the person and the 73% absorption by inhalation. In addition, it is taken into account that the NOAEL was derived from animal studies and an increase in the effects after long-term exposure cannot be ruled out. This would result in a concentration at the workplace of 2.9 mg/m^3 and, using the preferred value

approach, 2 mg/m³ for the inhalable fraction. The vapour saturation concentration of **ditridecyl phthalate** is about 7.2×10^{-7} mg/m³, that of **diisotridecyl phthalate** < 0.2 mg/m³. The substances would thus occur as an aerosol at this concentration. As the aerosol is considered responsible for the critical effects in the case of di-*n*-butyl phthalate (documentation "Di-*n*-butylphthalate" 2013), a MAK value has not been derived due to the lack of inhalation studies. Peak limitation is not applicable.

Prenatal toxicity. In a combined study of toxicity after repeated exposure and reproductive/developmental toxicity of **ditridecyl phthalate** in rats, no significant treatment-induced effects on the number of offspring, the sex ratio, body weights, external malformations and the survival of the offspring up to day 4 of lactation were observed. The NOAEL for foetotoxicity was the highest dose tested of 250 mg/kg body weight and day (CPSC 2011).

In a developmental toxicity study with Sprague Dawley rats given gavage doses of **ditridecyl phthalate** of up to 1000 mg/kg body weight and day from gestation days 6 to 20, no developmental or maternal toxicity was observed. There were no substance-induced effects on foetal anogenital distance (AGD) (Saillenfait et al. 2013).

As a MAK value cannot be derived, the substances are not classified in a pregnancy risk group.

Carcinogenicity. There are no carcinogenicity studies.

The studies available for **diisotridecyl phthalate** and **ditridecyl phthalate** provide no evidence of genotoxic potential. The combined study of toxicity after repeated administration and reproductive toxicity in rats found evidence of peroxisome proliferation in the liver. However, cyanide-insensitive palmitoyl-CoA oxidase activity, the marker enzyme for peroxisome proliferation, was not observed. There are no other studies of the mechanism of action.

Due to their chain lengths, **diisotridecyl phthalate** and **ditridecyl phthalate** are relatively similar in structure to diisodecyl phthalate, which has been evaluated by the Commission (documentation "Diisodecyl phthalate, mixture of isomers" 2011). Diisodecyl phthalate causes peroxisome proliferation and at most slight toxic effects on the testes. The studies of carcinogenicity that are available were not included in the evaluation because of numerous inadequacies. Diisodecyl phthalate was classified in Carcinogen Category 3B based on evidence that it has a similar mechanism of action in the target organ liver to that of di(2-ethylhexyl) phthalate (DEHP), a substance classified in Carcinogen Category 4. Therefore, by analogy with DEHP, a spectrum of tumour-inducing activity is assumed also for **diisotridecyl phthalate** and **ditridecyl phthalate** (documentation "Diisodecyl phthalate, mixture of isomers" 2011).

On the basis of their structure and the data available, the mechanism of action of **diisotridecyl phthalate** and **ditridecyl phthalate** is probably similar to that of DEHP, a substance classified in Carcinogen Category 4. Diisotridecyl phthalate and ditridecyl phthalate may therefore induce carcinogenic effects. For this reason, diisotridecyl phthalate and ditridecyl phthalate are classified in Carcinogen Category 3B.

Germ cell mutagenicity. The available in vitro studies did not find evidence of a genotoxic potential for either **diisotridecyl phthalate** or **ditridecyl phthal-**

ate. A micronucleus test with intraperitoneal injection of mice with **diisotridecyl phthalate** yielded negative results. There are no germ cell studies. The substances were not classified in a category for germ cell mutagens.

Absorption through the skin. The results of a study in rats with the structurally similar diisodecyl phthalate were used to calculate an absorbed amount of 2.7 mg under standard conditions (Section 3). The same absorption value is assumed for **diisotridecyl phthalate** and **ditridecyl phthalate**. The systemically tolerable concentration in air is 2.9 mg/m^3 (see Section "Manifesto, MAK value"). Therefore, assuming 73% absorption by inhalation and a respiratory volume of 10 m^3, 21 mg would be absorbed by inhalation. Absorption through the skin thus amounts to less than 25% of the systemically tolerable amount and **diisotridecyl phthalate** and **ditridecyl phthalate** are not designated with "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Positive findings are not available for sensitization of the skin or airways by **diisotridecyl phthalate** or **ditridecyl phthalate**; the substances are thus not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

7 References

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completed 21 March 2018