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(4-Nonylphenoxy)acetic acid

MAK Value Documentation – Translation of the German version from 2020

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Keywords

(4-nonylphenoxy)acetic acid; irritation; reproductive toxicity; genotoxicity; anti-androgenic effect; anti-oestrogenic effect; hazardous substance

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated (4-nonylphenoxy)acetic acid [3115-49-9] considering all toxicological end points. Available publications and unpublished study reports are described in detail. In a combined repeated dose toxicity study with the reproduction / developmental toxicity screening test in rats, (4-nonylphenoxy)acetic acid led to hyperplasia of the forestomach at 60 mg/kg body weight and day. Effects on fertility and developmental toxicity were not observed in this study. (4-Nonylphenoxy)acetic acid is corrosive to the skin and eyes of rabbits. An inhalation study has not been performed. Therefore, possible irritant effects on the respiratory tract cannot be evaluated and a maximum concentration at the workplace (MAK value) cannot be determined. (4-Nonylphenoxy)acetic acid is not genotoxic. A carcinogenicity study has not been performed on (4-nonylphenoxy)acetic acid. Skin contact is not expected to contribute significantly to systemic toxicity. Clinical results and valid animal studies on sensitization are not available.

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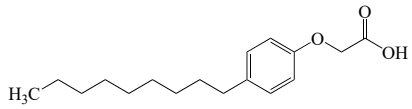
MAK value	**not yet established, see List of MAK and BAT Values, Section II b**
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–
Synonyms	(*p*-nonylphenoxy)acetic acid
Chemical name (IUPAC name)	2-(4-nonylphenoxy)acetic acid
CAS number	3115-49-9
Structural formula	
Molecular formula	$C_{17}H_{26}O_3$
Molar mass	278.39 g/mol
Melting point	–30 °C (ECHA 2017)
Boiling point at 1013 hPa	about 333 °C (extrapolated); 121 °C at 0.11 Pa (ECHA 2017)
Density at 20 °C	1.0288 g/cm³ (ECHA 2017)
Vapour pressure at 25 °C	0.000025 hPa (ECHA 2017)
log K_{OW} at 25 °C	undissociated: 5.4 to 5.8 (calculated) (ECHA 2017) at pH 5: 3.6 (ECHA 2017)
Solubility at 20 °C	40 mg/l water, pH 4.2 (ECHA 2017)
pKa value at 25 °C	3.1 to 3.79 (calculated) (ECHA 2017)
1 ml/m³ (ppm) ≙ 11.550 mg/m³	**1 mg/m³ ≙ 0.086 ml/m³ (ppm)**
Stability	no data
Production	no data
Purity	no data (ECHA 2017)
Impurities	4-nonylphenol, branched (CAS number: 84852-15-3) (no other details; ECHA 2017)
Use	anti-corrosive in lubricants

The documentation is based primarily on the REACH registration dataset publicly available (ECHA 2017).

There are no data available for concentration levels in lubricants.

1 Toxic Effects and Mode of Action

(4-Nonylphenoxy)acetic acid is severely irritating to corrosive to the skin and eyes of rabbits.

In a combined study of the toxic effects of repeated oral doses and reproductive toxicity in rats carried out according to OECD Test Guideline 422, (4-nonylphenoxy)acetic acid induced hyperplasia of the squamous epithelium of the forestomach in both sexes at dose levels of 60 mg/kg body weight and day and above; this was probably an effect of the acidity. T4 (thyroxine) concentrations in serum were significantly increased and the incidence of diffuse follicular hyperplasia and hypertrophy in the thyroid gland was increased at dose levels of 200 mg/kg body weight and day and above. In this study, there were no effects on fertility and developmental toxicity up to a (4-nonylphenoxy)acetic acid dose of 200 mg/kg body weight and day. At 200 mg/kg body weight and day, the reduction in body weights observed in female offspring was statistically significant on postnatal day 1, but not on postnatal day 4.

(4-Nonylphenoxy)acetic acid was not genotoxic in bacteria and mammalian cells in vitro and did not induce micronuclei in the bone marrow of Chinese hamsters given oral doses of up to 4000 mg/kg body weight and day on 2 consecutive days. There are no studies of carcinogenicity.

(4-Nonylphenoxy)acetic acid had anti-androgenic and anti-oestrogenic effects in vitro. A weakly positive reaction was obtained in a maximization test carried out in guinea pigs to investigate the sensitizing effects on the skin, but methodological shortcomings preclude a definitive assessment.

2 Mechanism of Action

To investigate the oestrogenic effects of the substance, a uterotrophic assay was performed with groups of 6 sexually immature female Wistar rats (20–22 days old) given (4-nonylphenoxy)acetic acid daily by gavage on 3 consecutive days at dose levels of 0, 10, 100, 200, 300 or 400 mg/kg body weight and day. Oestradiol benzoate (0.5 µg/animal, subcutaneous injection) was used as the positive control. The uteruses were weighed at necropsy 24 hours after the last application to determine possible effects. At dose levels of 200, 300 and 400 mg/kg body weight and day, the body weight gains were reduced to 79%, 56% and 63%, respectively, of the values obtained in the control animals. However, there were no significant effects on the final body weights nor substance-related clinical findings. A significant, 1.25-fold and 1.3-fold increase was observed in the absolute and relative uterine weights of the animals of the high dose group. A 3.76-fold and 3.82-fold increase in uterine weights was detected in the positive control with oestradiol benzoate, but no effects on body weights or body weight gains. (4-Nonylphenoxy)acetic acid induced weak oestrogenic effects in the uterotrophic assay (ICI Americas Inc 1996).

In a study carried out in 2012, the androgenic and anti-androgenic potential of (4-nonylphenoxy)acetic acid (purity > 99%) was investigated using the yeast androgen screening assay (YAS). The yeast cells were stably transformed with the human androgen receptor and the β-galactosidase reporter gene. Receptor binding or blocking can provide evidence of the androgenic and anti-androgenic potential of a test substance. Compared with dihydrotestosterone, (4-nonylphenoxy)acetic acid showed no androgenic activity. However, compared with hydroxyflutamide, (4-nonylphenoxy)acetic acid showed clear anti-androgenic activity at 10^{-5} mol/l and above. No cytotoxicity was observed (ECHA 2017).

The oestrogenic and anti-oestrogenic potential of (4-nonylphenoxy)acetic acid (purity > 99%) was investigated in yeast cells in the corresponding assay (YES = yeast oestrogen screening assay) with the human oestrogen receptor and β-galactosidase reporter gene. Compared with 17β-oestradiol, (4-nonylphenoxy)acetic acid showed no oestrogenic activity, but, compared with hydroxytamoxifen, slight anti-oestrogenic activity at 10^{-5} mol/l and above. No cytotoxicity was observed (ECHA 2017).

3 Toxicokinetics and Metabolism

There are no studies available.

No data are available for skin penetration. (4-Nonylphenoxy)acetic acid is corrosive to the skin. According to the Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (Regulation (EC) No. 1272/2008), this type of substance is assumed to induce skin irritation at concentrations of 1% and above; therefore, a 0.5% formulation is not expected to cause irritation. The saturation concentration is much lower at 40 mg/l water.

Flux values of 19, 0.5, 0.3 and 0.56 µg/cm^2 and hour were calculated for a saturated aqueous solution of (4-nonylphenoxy)-acetic acid with a log K_{OW} of 3.6 and a pH of 5 (skin has a pH of 5.5) (ECHA 2017) using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993), Wilschut et al. (1995) and IHSkinPerm (ten Berge 2009), respectively. Assuming the exposure of 2000 cm^2 of skin (surface area of hands and forearms) for one hour, this would be equivalent to the absorption of 38, 1, 0.6 and 1.2 mg, respectively.

4 Effects in Humans

There are no data available.

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 study carried out in the 1980s in male and female Wistar rats determined an LD_{50} for (4-nonylphenoxy)acetic acid (purity: "commercial-grade quality") of 1674 mg/kg body weight. Groups of 5 male and 5 female rats were given gavage doses of 1000, 2000, 3000 and 5000 mg/kg body weight dissolved in polyethylene glycol and were then observed for 14 days. One female rat died after exposure to the low dose of 1000 mg/kg body weight, 3 male and 3 female rats died after 2000 mg/kg body weight and all exposed animals died within 6 days after exposure to the two high doses. Sedation, rales, dyspnoea, ataxia, abdominal position, lateral position, hunched posture and ruffled fur were observed in all exposed groups. The primary findings in the gross-pathological examination were mottled lungs with foam excretion, reddened stomachs with whitish content, meteorism in the stomach and intestines, reddened intestines filled with whitish or yellowish contents, severely filled bladders and in some cases yellow-coloured adipose tissue (Ciba-Geigy Corp 1986; ECHA 2017).

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 a 14-day range-finding study published in 2012, groups of 4 male and 4 female Wistar Han rats (Crl:WI(Han)) were exposed to (4-nonylphenoxy)acetic acid (purity 97.4%) at dose levels of 0, 150 or 450 mg/kg body weight and day. The test substance was administered by gavage in a polyethylene glycol and water mixture (1:1). The control group was given the vehicle only. Mortality, clinical signs, body weights, feed consumption and organ weights were investigated and the kidneys, liver, spleen and adrenal glands underwent gross pathological examination. Testing was discontinued in the group exposed to 450 mg/kg body weight and day after 7 days because of severe toxicity. In addition to severe clinical signs of toxicity, a decrease in body weights and absolute and relative feed consumption was observed. Neither mortality nor clinical signs of toxicity or effects on feed consumption were observed at 150 mg/kg body weight and day. At the end of the treatment period (days 10 and 14), the body weight gains in the females were slightly lower than those in the control animals. A slight decrease in the number of reticulocytes in the females of the 150 mg/kg group was regarded as not toxicologically relevant. In addition, the glucose levels were increased in the males, as were the alanine aminotransferase and alkaline phosphatase activities in the females, while lower levels of bile acids were detected in the males. The relative liver weights were slightly increased in the animals at 150 mg/kg. Haematological and clinico-chemical examinations were not performed and the organ weights were not determined in the animals of the high dose group. Gross-pathological findings were observed only in the animals of the high dose group. In the majority of the animals, the forestomach was found to have an irregular surface, while a few had gelatinous contents in the gastrointestinal tract and isolated dark red foci on the stomach glandular mucosa (ECHA 2017).

In a combined study of the toxic effects of repeated oral doses and reproductive toxicity carried out in 2012 according to OECD Test Guideline 422, (4-nonylphenoxy)acetic acid (purity 97.4%) was given daily by gavage to 10 male and 10 female Crl:WI(Han) rats per dose group. The doses were selected based on the range-finding study (see above) and were 0, 20, 60 or 200 mg/kg body weight and day in a mixture of polyethylene glycol and water (1:1). The males were exposed for a total of 29 days beginning 2 weeks before mating and continuing through mating up to necropsy. The females were exposed for a total of 43 to 56 days beginning 2 weeks before mating and continuing through mating and gestation up to day 4 of lactation. Mortality did not occur during the study. Rales, piloerection, hunched posture and tremor were noted on isolated days in individual animals of the high dose group. As the incidence was limited, these were not considered to be toxicologically relevant. A slight decrease in body weight gains was observed in both sexes before and during mating. A slight, but significant decrease in body weight gains was observed in the males of the high dose group on day 8 of the mating period. The females exhibited slight body weight loss on day 8 of the study and slightly decreased body weight gains on day 1 of the mating period. Related changes in feed consumption were not observed.

The erythrocyte count and the haematocrit values were significantly lower in the males at 60 mg/kg body weight and day and above. The authors considered these findings not toxicologically relevant. In Table 1, the haematological parameters determined in the control animals of the study are listed together with those of 3 additional control groups of the same test laboratory and the same testing period. Compared with the values for the animals of these 3 other control groups, the values of the control group for (4-nonylphenoxy)acetic acid were comparatively high. On the basis of the haematological parameters determined in the animals of the 3 additional control groups of the test laboratory, no effects on the erythrocyte count and haematocrit values were evident. The reticulocyte count and the red blood cell distribution width (RDW) were increased in the females at 200 mg/kg body weight and day. However, when the reticulocyte values of the control group of the (4-nonylphenoxy)acetic acid study were compared with those of the 3 other control groups, the values were found to be comparatively low. If the values determined for the 3 control groups of the test laboratory are used as the basis for comparison, no effects on the reticulocyte count are apparent. At 200 mg/kg body weight and day, the T4 concentrations were increased in both sexes at all sampling times; in addition, the cholesterol levels were increased in the females. Hearing ability, pupillary reflex, static righting reflex and grip strength were unchanged by exposure to the substance.

At 60 mg/kg body weight and day, the absolute and relative weights of the thyroid gland were increased in the females, while the absolute spleen weights were increased in the males. However, the increases were not statistically significant at the high dose of 200 mg/kg body weight and day (see Table 2). In addition, the absolute kidney weights were found

to be increased in the males at doses of 60 mg/kg body weight and day and above (independent of the dose) and the relative kidney weights at 200 mg/kg body weight and day. At 200 mg/kg body weight and day, increases in the absolute and relative weights of the liver, thyroid gland and kidneys were determined in the males and in the relative liver and uterine weights in the females. With the exception of the thyroid gland, histological changes were not found in the affected organs and in some cases the changes in the organ weights were not dependent on the dose. The relevance of these findings is therefore questionable.

In the gross-pathological examination, several reddish to dark red foci were visible in the stomach of 4 males and the forestomach of 1 male and 1 female of the high dose group was found to have an irregular surface. This was attributed to effects induced by the acidity of the test substance. Histopathological findings were reported in the stomach in both sexes and in the thyroid gland in the females. Hyperplasia of the squamous epithelium of the forestomach was observed in 1 of 5 males and in 2 of 5 females (3 × minimal) at 60 mg/kg body weight and day and in 4 of 9 males (1 × minimal, 2 × mild, 1 × moderate) and in 5 of 5 females (1 × minimal, 3 × mild, 1 × moderate) at 200 mg/kg body weight and day (see Table 3).

Minimal to slight bleeding in the glandular stomach was observed in 4 of 9 males of the high dose group. Minimal diffuse follicular hyperplasia and hypertrophy were observed in the thyroid gland of 1 of 5 females both at 20 and at 60 mg/kg body weight and day; these effects were found in 2 of 5 animals of the control group. At 200 mg/kg body weight and day, minimal diffuse follicular hyperplasia and hypertrophy were determined in 3 animals and a mild grade was observed in 2 of 5 animals. According to the authors of the study, the NOAEL (no observed adverse effect level) was 60 mg/kg body weight and day (BASF SE 2019; WIL Research Europe B.V. 2012). In view of the initial signs of irritation in the forestomach of the animals at 60 mg/kg body weight and day, the Commission regards the NOAEL to be 20 mg/kg body weight and day.

Tab. 1 Haematological findings in rats (n = 5) after repeated oral administration of (4-nonylphenoxy)acetic acid (BASF SE 2019; WIL Research Europe B.V. 2012)

Parameters (units)	Sex	Controls of the test laboratory [a)]	Dose (mg/kg body weight)			
			0	20	60	200
erythrocytes (10^{12}/l)	♂	8.40, 8.29, 8.25	8.97	8.78	8.42 **	8.54 *
	♀		7.54	7.25	7.46	7.25
haematocrit (l/l)	♂	0.42, 0.42, 0.42	0.464	0.452	0.438 **	0.437 **
	♀		0.423	0.403	0.408	0.400
reticulocytes (% RBC)	♂		2.1	2.3	2.5	2.1
	♀	5.8, 6.2, 6.4	4.6	5.5	5.6	6.4 +
RDW (%)	♂		12.8	13.0	14.4	15.1
	♀		14.0	16.3	15.5	18.8 *

RBC: red blood cells; RDW: red blood cell distribution width

[a)] The laboratory that carried out this study performed three additional studies using the same protocol (OECD 422) in the preceding and following year. The findings determined in the 3 other control groups are listed here (BASF SE 2019).

*/**On the basis of the pooled variance, Dunnett's test was significant at 5% (*) and 1% (**)

+ Steel's test was significant at 5%

Tab. 2 Effects on the absolute (in g) and relative (in %) organ weights of rats (n = 5) after repeated oral administration of (4-nonylphenoxy)acetic acid (WIL Research Europe B.V. 2012)

Organ	Sex	absolute weight in g relative weight in %	Dose (mg/kg body weight)			
			0	20	60	200
liver	♂	absolute	7.50	8.44	8.80	9.05 *
		relative	2.24	2.48	2.46	2.66 **
	♀	absolute	7.94	8.67	7.86	8.90
		relative	3.49	3.58	3.47	4.00 *
thyroid gland	♂	absolute	0.024	0.024	0.024	0.032 **
		relative	0.007	0.007	0.007	0.009 *
	♀	absolute	0.020	0.021	0.025 *	0.023
		relative	0.009	0.008	0.011 *	0.010
kidneys	♂	absolute	2.10	2.33	2.53 *	2.47 *
		relative	0.63	0.68	0.71	0.73 *
	♀	absolute	1.64	1.80	1.58	1.71
		relative	0.72	0.74	0.70	0.77
spleen	♂	absolute	0.528	0.579	0.655 *	0.598
		relative	0.157	0.170	0.183	0.176
	♀	absolute	0.506	0.573	0.479	0.628
		relative	0.223	0.238	0.212	0.279
uterus	♀	absolute	0.419	0.473	0.422	0.504
		relative	0.185	0.195	0.186	0.227 *

*/**On the basis of the pooled variance Dunnett's test was significant at 5% (*) and 1% (**)

Tab. 3 Hyperplasia of the squamous epithelium of the forestomach in rats after repeated oral administration of (4-nonylphenoxy)-acetic acid (WIL Research Europe B.V. 2012)

Dose (mg/kg body weight and day)	Sex (number of animals tested)	Number (incidence in %) of animals and degree of hyperplasia of the squamous epithelium		
		minimal	mild	moderate
0	♂ (n = 5)	0	0	0
	♀ (n = 5)	0	0	0
20	♂ (n = 5)	0	0	0
	♀ (n = 5)	0	0	0
60	♂ (n = 5)	1 (20)	0	0
	♀ (n = 6)	2 (33)	0	0
200	♂ (n = 9)	1 (11)	2 (22)	1 (11)
	♀ (n = 5)	1 (20)	3 (60)	1 (20)

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 from 1983 carried out according to OECD Test Guideline 404, 0.5 ml (4-nonylphenoxy)acetic acid (purity: "commercial-grade quality") was applied to the shaved skin of 3 female New Zealand White rabbits for 4 hours under semi-occlusive conditions. The skin reactions were assessed after 1, 24, 48 and 72 hours. After 1 hour, grade 2 ery-

thema (on a scale up to 4) was observed in all animals, grade 3 after 24 hours and grade 4 after 48 and 72 hours. This is evidence of a corrosive effect. Slight oedema was determined after 1 hour (grade 2 on a scale up to 4) and grade 3 oedema after 24 to 72 hours. The primary irritation index over the entire study period was 5.92 on a scale of up to 8.0. (4-Nonylphenoxy)acetic acid was considered to be severely irritating. Testing was discontinued after 72 hours because of the severe skin reactions. The manufacturer has classified the substance in "skin corrosive category 1B" (ECHA 2017).

5.3.2 Eyes

In a study from 1983 carried out according to OECD Test Guideline 405, 0.1 ml of (4-nonylphenoxy)acetic acid (purity: "commercial-grade quality") was instilled into the conjunctival sac of 1 eye in 3 male New Zealand White rabbits. The eyes were examined for reactions after 1, 24, 48 and 72 hours. (4-Nonylphenoxy)acetic acid was found to be corrosive. Testing was discontinued after 72 hours because of the severity of the reactions (ECHA 2017).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a maximization test according to OECD Test Guideline 406, groups of 10 female and 10 male Pirbright White guinea pigs were treated for induction intradermally with a 1% formulation of (4-nonylphenoxy)acetic acid in sesame oil and topically with a 3% formulation of the substance in petrolatum. The challenge treatment was performed with a 0.3% formulation of (4-nonylphenoxy)acetic acid in petrolatum. At the 24-hour and 48-hour readings, a slight erythematous reaction was observed in 15 of 20 animals at each time point and slight erythema in 10 and 5 of the animals, respectively. Of the 10 control animals pre-treated with the vehicle and adjuvant, none produced an erythematous or oedematous reaction to the test formulation (Ciba-Geigy Ltd 1985). However, as this maximization test used a batch described as "commercial-grade quality" without any further information about its content or purity, the validity of the findings is questionable.

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 combined study of the toxic effects of repeated oral doses and reproductive toxicity carried out in 2012 according to OECD Test Guideline 422, (4-nonylphenoxy)acetic acid (purity 97.4%) was given by gavage to groups of 10 male and 10 female Crl:WI(Han) rats in a polyethylene glycol and water mixture (1:1) at doses of 0, 20, 60 or 200 mg/kg body weight and day. The males were exposed for a total of 29 days, beginning 2 weeks before mating and continuing through mating up to necropsy. The females were exposed for a total of 43 to 56 days beginning 2 weeks before mating and continuing through mating and gestation and up to postnatal day 4. The doses were selected based on a 14-day range-finding study. The findings in the parent animals are discussed in Section 5.2.2. The indices for mating, fertility and conception, number of days to mating, number of corpora lutea, implantation sites and gestation index were not affected by the treatment. According to the authors of the study, the NOAEL was 60 mg/kg body weight and day for parental toxicity and 200 mg/kg body weight and day for fertility (WIL Research Europe B.V. 2012). As a result of the initial signs of irritation in the forestomach of the animals at 60 mg/kg body weight and day, the Commission regards the NOAEL for the parent animals to be 20 mg/kg body weight and day (see Section 5.2.2).

5.5.2 Developmental toxicity

A combined study of the toxic effects of repeated oral doses and reproductive toxicity was carried out with Crl:WI(Han) rats according to OECD Test Guideline 422 (see Section 5.5.1). The findings in the parent animals are discussed in Section 5.2.2. No changes were observed in the gestation index and length of gestation, parturition and raising of the offspring by the dams. Also the number of live offspring, survival index, sex ratio and gross-pathological findings after birth were not adversely affected by the treatment. In the first 5 days of the postnatal period, 6 offspring (1 to 2 per litter) in the 200 mg/kg group died or disappeared (cannibalism). This finding is not unusual, but the incidence was higher than in the other groups. The mean incidence for postnatal losses was 0.6 in the 200 mg/kg group and was within the historical control incidence of the test laboratory (1.0). The number of live offspring was slightly higher in the 200 mg/kg group than in the other groups. A slight, dose-dependent shift in the sex ratio was observed. At 200 mg/kg body weight and day, the sex ratio was 40% female to 60% male offspring. The body weights of the female offspring were significantly reduced on postnatal day 1 at 200 mg/kg body weight and day; however, this decrease was no longer statistically significant on postnatal day 4. According to the authors of the study, the NOAEL was 60 mg/kg body weight and day for parental toxicity and 200 mg/kg body weight and day for developmental toxicity (WIL Research Europe B.V. 2012). As a result of the initial signs of irritation in the forestomach of the animals at 60 mg/kg body weight and day, the Commission considers the NOAEL for parent animals to be 20 mg/kg body weight and day (see Section 5.2.2).

5.6 Genotoxicity

5.6.1 In vitro

A mutagenicity test published in 1984 investigated (4-nonylphenoxy)acetic acid (purity: "commercial-grade quality") at concentration levels of 0, 20, 80, 320, 1280 or 5120 µg/plate in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 with and without the addition of metabolic activation. The substance induced cytotoxic effects at high concentrations (no other details) and precipitated at 1280 and 5120 µg/plate. Mutagenicity was not observed. The functioning of the test system was verified by the positive controls (ECHA 2017).

In 2013, an HPRT test was carried out in V79 cells according to OECD Test Guideline 476. In the first experiment, (4-nonylphenoxy)acetic acid (purity: 97.4%) was tested at concentrations of up to 22 µg/ml and 176 µg/ml for 4 hours without and with metabolic activation, respectively. The second experiment tested concentrations of up to 132 µg/ml (24 hours without metabolic activation) and of up to 132 µg/ml (4 hours with metabolic activation). In each test, the substance induced marked cytotoxicity at the highest concentrations. After treatment for 4 hours with metabolic activation, precipitates were observed in the first experiment at concentrations of 132 µg/ml and above and in the second experiment at concentrations of 88 µg/ml and above. Gene mutations were not induced in the HPRT gene. The three-fold mutation frequency of the concurrent control was exceeded in the second experiment at 5.5 and 44 µg/ml in one of two parallel cultures with metabolic activation in each case. This was not regarded as biologically relevant because of the low values in the concurrent control (6.7 mutant colonies/10^6 cells). The functioning of the test system was verified by the positive controls (ECHA 2017).

5.6.2 In vivo

In a study from 1985, (4-nonylphenoxy)acetic acid (purity "commercial-grade quality") was given to groups of 6 male and 6 female Chinese hamsters on 2 consecutive days in gavage doses of 0, 1000, 2000 or 4000 mg/kg body weight and day. Samples from the bone marrow were investigated for micronuclei 24 hours after administration of the last dose. In accordance with the test guideline valid at that time, 1000 cells per animal were examined. The highest dose of 4000 mg/kg body weight and day was lethal for 1 male animal. (4-Nonylphenoxy)acetic acid did not lead to an increased incidence of micronuclei. The functioning of the test system was verified by the positive controls (ECHA 2017).

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value/classification)

The critical effects are the severe irritation to corrosion of the skin and eyes of rabbits. No data are available for the toxic effects in humans.

MAK value. No inhalation studies are available for (4-nonylphenoxy)acetic acid. In 2012, a combined study of the toxic effects of repeated oral doses and reproductive toxicity in rats carried out according to OECD Test Guideline 422 (WIL Research Europe B.V. 2012) determined a NOAEL of 20 mg/kg body weight and day for the parent animals. 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 5 days per week exposure at the workplace (7:5), the species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 49 mg/m^3 (4.25 ml/m^3). As this value was calculated on the basis of a NOAEL determined in animal studies (1:2) and after extrapolation of this value to chronic exposure (1:4, as the length of the study lies between that of subacute and subchronic studies), a concentration of 6.13 mg/m^3 (0.53 ml/m^3) has been derived, which, after applying the Preferred Value Approach, is equivalent to a MAK value of 0.5 ml/m^3. However, as (4-nonylphenoxy)acetic acid is severely irritating to corrosive to the skin and eyes and there are no inhalation studies of the local effects in the respiratory tract, a MAK value cannot be derived. (4-Nonylphenoxy)acetic acid has therefore been assigned to Section IIb of the List of MAK and BAT Values. Peak limitation is not applicable.

Prenatal toxicity. Classification in a Pregnancy Risk Group is not applicable because a MAK value cannot be derived.

Carcinogenicity and germ cell mutagenicity. No germ cell mutagenicity tests are available. (4-Nonylphenoxy)-acetic acid was not genotoxic in vitro in bacteria and mammalian cells and did not induce micronuclei in the bone marrow of Chinese hamsters given oral doses of up to 4000 mg/kg body weight and day on 2 consecutive days. There are no studies of carcinogenicity. On the basis of the available data, there is no cause to classify (4-nonylphenoxy)acetic acid in a category for germ cell mutagens or carcinogens.

Absorption through the skin. On the basis of a model calculation (Section 3), the maximum amount absorbed through the skin is estimated to be 38 mg for humans after exposure to a saturated aqueous solution under standard conditions (surface area of skin: 2000 cm^2, exposure: 1 hour).

As the NOAEL was derived on the basis of local irritation in the forestomach after gavage administration, the systemic NOAEL is 60 mg/kg body weight and day. Using the same calculation steps as above, the systemically tolerable concentration for humans is 19 mg/m^3. At 100% absorption by inhalation and a respiratory volume of 10 m^3, the tolerable intake level is 190 mg. Absorption through the skin is therefore less than 25% of the systemically tolerable amount and the substance is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data available for sensitization of the skin or airways in humans. The positive findings determined in a maximization test in guinea pigs are of questionable validity, also in view of structural considerations. In addition, the test results were only weakly positive and the purity of the tested batch is unclear. Therefore, (4-nonylphenoxy)acetic acid has not been designated with either "Sa" or "Sh" (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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