FOREWORD INTRODUCTION

3-Hydroxy-2-naphthoic acid

CAS: 92-70-6

SIDS Initial Assessment Report

For

SIAM 19

Berlin, Germany; 19-22 October 2004

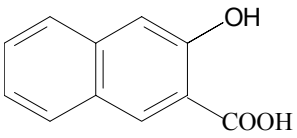
1. Chemical Name:	3-Hydroxy-2-naphthoic acid
2. CAS Number:	92-70-6
3. Sponsor Country:	Germany / Japan Contact Point: Federal Environmental Agency (UBA) Seeckstr. 6-10 D-13581 Berlin
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	In the first stage of the process Clariant was sponsor company. As production has stopped at this company, the industry sponsor has not taken an active role in the further assessment process.
• Process used	Environmental assessment was performed by Federal Environmental Agency (UBA); Human Health assessment was performed by BUA (Advisory Committee on Existing Chemicals) and reviewd by BgVV. After that the Japanese sponsor reviewed the complete assessment.
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	The substance was selected in phase 3 of the OECD-SIDS programme by Germany. Japan has performed the reproductive toxicity study and became so a co-sponsor for this substance.
7. Review Process Prior to the SIAM:	SIDS testing plan was discussed at the 3rd SIDS Review Meeting (September 1993). There, it was agreed that tests on acute toxicity to daphnids, chromosomal aberration and reproductive toxicity should be performed.
8. Quality check process:	As basis for the SIDS-Dossier the non-confidential IUCLID from the European Chemicals Bureau was used. All information that could not be reproduced was deleted (mainly chapter 1). If this information was used in the assessment, reference to the ECB-IUCLID is made. All other data have been checked and validated by UBA and BUA except the studys on toxicity to fish, daphnia and algae performed by MOE, Japan which have been validated by the Japanese Co-Sponsor.

9. Date of Submission:

10. Date of last Update:

11. Comments: The assessment was discussed at SIAM 15 where the Human Health part was agreed. The environmental part could not be finalised because no valid algae toxicity test was available. After SIAM 15 the Japanese Co-Sponsor performed the missing algae study as well as additional studies on fish, and daphnia and the environmental assessment was revised.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	92-70-6
Chemical Name	3-Hydroxy-2-naphthoic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral LD50 of 3-Hydroxy-2-naphthoic acid in rats was 823-1040 mg/kg bw. Clinical signs included reduced activity, accelerated breathing, closure of eyes, and diarrhoea. Gastro-intestinal irritation and dark or mottled livers were seen in the animals that had died during the studies.

A 10% solution of 3-Hydroxy-2-naphthoic acid (approx. 2000 mg/kg bw) was lethal to guinea pigs when applied dermally for 24 hours under occlusive conditions.

Moistened 3-Hydroxy-2-naphthoic acid was slightly irritating to the skin of rabbits in a test performed in accordance with OECD TG 404. Skin necroses and subcutaneous hemorrhages were observed in guinea pigs after occlusive exposures for 24 hours to the 10-12% solutions in mixtures of acetone and olive oil or corn oil. It caused serious damage to the eyes of rabbits (corneal vascularization/opacity) in tests performed in accordance with OECD TG 405. It may also have caused skin and upper respiratory tract irritation in workers.

3-Hydroxy-2-naphthoic acid has skin sensitisation potential.

After repeated administration to rats by the oral route for 28 days, there were indications of a possible effect on the adrenals in females at dose levels of 60 mg/kg bw/day and above. The only effects observed in males were a significantly reduced serum phosphate level and increased levels of bilirubin in serum and urine at a dose level of 300 mg/kg bw/day. The same findings, and, in addition, increased liver weights were reported for females at 300 mg/kg bw/day. NOEL (male): 60 mg/kg bw/day; NOEL (female): 12 mg/kg bw/day.

Poorly documented studies in rats involving repeated administration by the inhalation route gave indications of an effect on the kidneys (kidney necroses were reported after 10-days inhalation of 100 mg/m3).

3-Hydroxy-2-naphthoic acid was judged non- mutagenic in three Ames bacterial tests in Salmonella typhimurium and Escherichia coli strains, but it caused chromosomal damage in V79 hamster cells in vitro (only in the absence, but not in the presence of metabolic activation). No clastogenic activity, and no toxicity was observed in vivo in bone marrow cells of hamsters, dosed with the maximum recommended dose of 2000 mg/kg bw, suspended in starch mucilage. Due to severe limitations (only 50 metaphases were examined per animal and there was no indication that the target tissue was reached by the chemical), the available in vivo study is not sufficient to assess whether the in vitro mutagenic activity is reproduced in vivo.

3-Hydroxy-2-naphthoic acid was tested for its reproductive toxicity in a one-generation study according to OECD TG 415. The administration of the test substance had no adverse effect on the reproductive abilities of the parental generation. At a dose level of 200 mg/kg bw/day, the body weight of the offspring was decreased. Growth retardation and malformations (brachyury, kinked tail) were observed in the offspring of few litters at a maternally toxic dose (200 mg/kg bw/day). No Effect Level (NOEL) for reproductive toxicity: 200 mg/kg bw/day (highest tested dose); NOEL for toxicity to the offspring: 50mg/kg bw/day. The NOEL for systemic toxicity in males was 12.5 mg/kg bw/day (forestomach lesions at 50 mg/kg bw/day). The NOEL for systemic toxicity in females was 50 mg/kg bw/day (reduced body weight gain, forestomach lesions at 200 mg/kg bw/day).

Environment

3-Hydroxy-2-naphthoic acid has a calculated water solubility of 474 mg/l, a calculated vapor pressure of < 1.4 Pa and calculated log Kow values in the range of 3.4 – 3.59. The calculated data available are estimated for the undissociated acid. As 3-Hydroxy-2-naphthoic acid has a pKa-value of 2.8, under environmental relevant pH conditions the substance is completely dissociated. That means that the physico-chemical properties that are derived for the undissociated acid are not valid for the ionized substance.

The environmental distribution of the substance cannot be estimated with a fugacity model as the available physico-chemical properties were determined for the undissociated acid and not for the dissociated form that is present under environmental relevant pH conditions. However, as both volatilisation and adsorption are not expected for the dissociated substance, it can be assumed that the hydrosphere is the main target compartment for 3-hydroxy-2-naphthoic acid. This is confirmed by a Mackay I model run for the sodium salt.
3-Hydroxy-2-naphthoic acid is not readily biodegradable as was shown in a test according to OECD 301 C (1.3 % after 14 days). In a Zahn-Wellens test (OECD 302 B) with adapted inoculum the chemical was inherently biodegradable (85 % after 21 days). In a 42d bioaccumulation study with Cyprinus carpio BCF values of < 0.5 resp. < 4 were found for 3-hydroxy-2-naphthoic acid concentrations of 1 mg/l and 0.1 mg/l. Therefore, 3-hydroxy-2-naphthoic acid has no potential for bioaccumulation.

For 3-hydroxy-2-naphthoic acid there are short-term tests with fish, daphnids and algae available. In addition, a long-term test with *Daphnia magna* was performed. The following effect values were found:

Brachydanio rerio: 96h-LC_{50} = 68mg/l, *Daphnia magna*: 48h-EC_{50} = 32.9 mg/l, *Pseudokirchneriella subcapitata*: 72h-E_rC_{50} = 65.3 mg/l, 72h-EbC50=26.1 mg/l; 72h-NOEC = 6.8 mg/l; *Daphnia magna*: 21d-NOEC = 10.4 mg/l.

With an assessment factor of 50 a PNECaqua of 136 µg/l was derived from the lowest available NOEC of 6.8 mg/l found for green algae.

Exposure

In the EU the production and import volume is in the range of 10,000 to 50,000 t/a. The worldwide production capacity for 3-hydroxy-2-naphthoic acid is reported to 30,000 t/a . 3-Hydroxy-2-naphthoic acid is mainly used as intermediate for the production of dyes and pigments. Further uses are as intermediate for insecticides and pharmaceuticals.

Occupational exposure may occur during production and processing of 3-hydroxy-2-naphthoic acid, mainly via the dermal route. Workplace measurements are available from one European production plant, ranging up to 1.23 mg/m^3 (mean value: 0.35 mg/m^3). No exposure information is available with regard to processing sites.

3-Hydroxy-2-naphthoic acid is a chemical intermediate for the production of dyes and pigments, which may also be used for pharmaceutical applications. A product containing 100% 3-Hydroxy-2-naphthoic acid is listed in the Swiss Product Register (2002) for industrial use (product category: developer/paints/dyes/laquers). No information on consumer products containing 3-Hydroxy-2-naphthoic acid was located in the Danish, Swedish and Swiss Product Registers (2002) and for Germany.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work, because 3-Hydroxy-2-naphthoic acid was a potent in vitro clastogen in an assay without metabolic activation. Due to severe limitations of the available in vivo chromosomal aberration study (only 50 metaphases were examined per animal and there was no indication that the target tissue was reached by the chemical), it is not possible to finally assess whether the in vitro mutagenic activity is reproduced in vivo. A standard in vivo test (mouse bone marrow chromosome aberration test (OECD TG 475) or an erythrocyte micronucleus test (OECD TG 474)) should therefore be performed as post-SIDS work. It is noted that the chemical is a skin irritant, can cause serious damage to the eye, is a skin sensitiser and there are indications of a teratogenic potential.

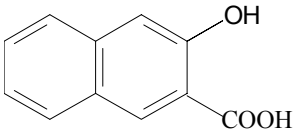
Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor Country (that reports that the only known use of the chemical in two OECD countries is as an intermediate, and relating to an unknown fraction of the global production volume), exposure to the environment is anticipated to be low, and therefore, this chemical is of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 92-70-6
IUPAC Name: 3-hydroxy-2-naphthoic acid
Molecular Formula: $C11H8O_3$
Structural Formula:



Synonyms: β-Hydroxynaphthoic acid

2-hydroxy-3-carboxynaphthalene

2-hydroxy-3-naphthoic acid

β-oxynaphthoic acid

BON

BONA

BONS

C.I. Developer 20

Developer BON

1.2 Purity/Impurities/Additives

degree of purity: > = 98.5 % w/w

Impurities: 2-naphthol, max 1%

1.3 Physico-Chemical properties

Water solubility:	474 mg/l (calculated for undissociated acid)
log Kow:	3.4 - 3.59 (calculated for the undissociated acid)
	0.17 (measured for the ionised form)
Vapor pressure:	< 1.4 Pa (calculated)
pKa:	2.8 (calculated)

No valid measured data about physico-chemical properties of 3-hydroxy-2-naphthoic acid available. The calculated data available are estimated for the undissociated acid. As 3-Hydroxy-2-naphthoic acid has a pKa-value of 2.8, under environmental relevant pH conditions the substance is completely dissociated. That means that the physico-chemical properties that are derived for the undissociated acid are not valid for the ionized substance.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

In the EU the production and import volume is in the range of 10,000 to 50,000 t/a (ECB, 2000). The worldwide production capacity for 3-hydroxy-2-naphthoic acid is reported to 30,000 t/a (Clariant, 2001). The production level of 3-hydroxy-2-naphthoic acid in Germany was 1,000-5,000 t in 1991. The only German manufacturer has stopped its production in 1996. In 2000, 1700 t were used by this site.

3-Hydroxy-2-naphthoic acid is mainly used as intermediate for the production of dyes and pigments. Further uses are as intermediate for insecticides and pharmaceuticals (ECB, 2000)

The substance is not listed in the Danish and Swedish product registers (June 2002). In the Swiss product register (May 2002) one product is listed for industrial use in the category "developer, paints, dyes and laquers" with a content of up to 100%.

Releases into the environment may occur during production and processing of 3-hydroxy-2-naphthoic acid. During production and processing of the substance by one German chemical plant, 10 t/a were emitted into the waste water and 400 kg/a into the air. As the production of 3-hydroxy-2-naphthoic acid has stopped in 1996, this source of exposure does not longer exists. There are no data available on the environmental releases from processing at this site. From an Italian production site the information is available that the concentration of 3-hydroxy-2-naphthoic acid in the effluent of the waste water treatment plant is below the detection limit of 0.01 mg/l (ECB, 2000). There are no further emission data available.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

The environmental distribution of 3-hydroxy-2-naphthoic acid cannot be modelled with a fugacity model as the available calculated physico-chemical properties were determined for the undissociated acid and not for the dissociated form that is present under environmental relevant pH conditions. However, as both volatilisation and adsorption are not expected for the dissociated substance, it can be assumed that the hydrosphere is the main target compartment for 3-hydroxy-2-naphthoic acid. This is also confirmed by a Mackay I model run for the sodium salt.

2.2.2 Photodegradation

The calculated half-life due to photochemical-oxidative degradation in the atmosphere by OH-radicals is about 15.9 hours.

2.2.3 Biodegradation

3-Hydroxy-2-naphthoic acid is not readily biodegradable as shown in a MITI-I test with non-adapted inoculum (OECD 301 C: 1.3 % after 14 d) (CITI, 1992). In a Zahn-Wellens test (OECD 302 B) conducted with industrial activated sludge a biodegradation of 85 % after 21 and 28 days was found. Elimination was not caused by adsorption (Hoechst, 1992a). From this test result it can be concluded that 3-hydroxy-2-naphthoic acid is inherently biodegradable by adapted inoculum. According to the model SIMPLETREAT, in industrial wwpts a removal rate of 0 % is predicted (no volatilization, no significant adsorption as shown in the Zahn-Wellens-test, $k_{deg} = 0\ h^{-1}$).

2.2.4 Bioaccumulation

In a 42d bioaccumulation study with *Cyprinus carpio* BCF values of < 0.5 resp. < 4 were found for 3-hydroxy-2-naphthoic acid concentrations of 1 mg/l and 0.1 mg/l (CITI, 1992). Therefore, 3-hydroxy-2-naphthoic acid has no potential for bioaccumulation.

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure may occur during production and processing of 3-hydroxy-2-naphthoic acid, mainly via the dermal route.

In Germany, the production of 3-hydroxy-2-naphthoic acid was stopped in 1996. No exposure information is available with regard to processing sites.Workplace measurements are available from one European production plant (7 unspecified workplaces, 29 samples): mean value =0.347 mg/m3, max. value = 1.229 mg/m3 (ECB, 2000). There was no information about the use of engineering controls or personal protective equipment.

3-Hydroxy-2-naphthoic acid is a chemical intermediate for the production of dyes and pigments, which may also be used for pharmaceutical applications. One single product is listed for industrial use in the Swiss Product Register (2002) in the category “developer, paints, dyes and laquers” with a content of up to 100%.

2.3.2 Consumer Exposure

No information on consumer products containing 3-hydroxy-2-naphthoic acid was located in the Danish Product Register (2002), and in the German CIVS database (BgVV, 2002).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No adequate data available.

3.1.2 Acute Toxicity

Inhalation

No data available.

Dermal

In a poorly documented, old and very limited study, a dose of 2000 mg/kg bw caused the death of a guinea pig, whilst 1000 mg/kg bw were non-lethal (Eastman Kodak, 1954). In this study, only one animal was used per dose level, and the exposure was for 24 hours under occlusive conditions. At the highest dose level (approximately 2000 mg/kg bw; applied as a 10% solution in acetone:corn oil) necroses were seen which covered about one half of the total application area.

Conclusion:

A 10% solution of 3-hydroxy-2-naphthoic acid (approx. 2000 mg/kg bw) was lethal to guinea pigs when applied dermally for 24 hours under occlusive conditions.

Oral

3-Hydroxy-2-naphthoic acid was tested for its acute toxicity in two studies performed in accordance with OECD TG 401. In these studies, an oral LD50 in the range between 823 and 1040 mg/kg bw was determined in rats of both sexes. Clinical signs included reduced activity, accelerated breathing, closure of eyes, and diarrhoea. All deaths occurred between 35 minutes and one day after exposure. Gastro-intestinal irritation and dark or mottled livers were seen in the animals that had died during the study, whilst the surviving animals were free of pathological changes at the end of the 14-day observation period (Hoechst AG, 1983a, 1984)). LD50 values in the range between 800 and 2450 mg/kg bw have been reported for the rat in other, poorly documented and limited studies and publications.

Conclusion:

The acute oral LD50 in rat was between 823-1040 mg/kg bw. Clinical signs included reduced activity, accelerated breathing, closure of eyes, and diarrhea. Gastro-intestinal irritation and dark or mottled livers were seen in the animals that had died during the studies.

3.1.3 Irritation

Skin Irritation

In a skin irritation study performed under semi-occlusive conditions according to OECD TG 404, the moistened test substance was slightly irritating to the skin of rabbits (Draize scores of 0.3 each for erythema and edema). Very slight erythema and edema (both barely perceptible) were observed 1 hour and 24 hours after removal of the patches. The effects were completely reversible within 48 hours (Hoechst AG, 1983b). When the substance was applied to guinea pigs as a 12% solution in a mixtures of acetone and olive oil, and held in contact with the skin for 24 hours under occlusive conditions, the skin became edematous, necrotic, and there was some subcutaneous hemorrhage. In three guinea pigs, treated similiarly with 5-20 ml/kg of a 10% solution in a mixture of acetone and corn oil, it produced from slight to moderate irritation up to necroses, depending on the dose (Eastman Kodak, 1954; 1958).

Conclusion:

Moistened 3-hydroxy-2-naphthoic acid was slightly irritating to the skin of rabbits in a test performed according to OECD TG 404. Skin necroses and subcutaneous hemorrhages were observed in guinea pigs after occlusive exposure for 24 hours to the 10-12% solution in a mixture of acetone and olive oil or corn oil.

Eye Irritation

In an eye irritation study performed according to OECD TG 405, the moistened test substance caused serious damage to the eyes of rabbits. 1 hour after application, swelling and conjunctival injection as well as secretion (clear, tinted by the test substance) were observed in all three animals. At 24, 48 and 72 hours, conjunctivitis and diffuse corneal opacities were found. One animal showed iritis at 24 and 48 hours. Mean Draize scores (24-72 h): corneal opacity: 1.1, iris: 0.2, conjunctivitis: 1.9, conjunctival swelling: 1.3. At 7 days after the application, corneal erosion and vascularization were observed in all animals. The effects were not reversible until study end (14 days after treatment) (Hoechst AG, 1983c).

Conclusion:

3-Hydroxy-2-naphthoic acid caused serious damage to the eyes of rabbits in a test performed in accordance with OECD TG 405 (corneal vascularization / opacity).

3.1.4 Sensitisation

Skin

Studies in Animals

3-Hydroxy-2-naphthoic acid (commercial grade) was sensitising in a modified guinea pig maximization test (Okada et al., 1985).(The deviation from the OECD TG 406 was that the epicutaneous challenge was performed under open (and not occlusive) conditions. Since the test gave a positive result, this modification is not considered to compromise the validity and reliability of the test. At challenge, 6 out of 9 animals had positive reactions towards the 1 % preparation in acetone, but did not react towards a 0.1 % preparation, indicating an elicitation threshold between 0.1 and 1%.

3-Hydroxy-2-naphthoic acid (purity 98.5%) was not sensitising in a guinea pig maximization test performed with only 10 animals (challenge concentration 0.25%) (Hoechst AG (1988b). Due to the small number of animals in the latter test, it cannot be concluded that 3-hydroxy-2-naphthoic acid is not a sensitizer; however, its potency may be low.

Studies in Humans

In humans, no skin sensitisation was seen when 36 subjects (28 healthy, 8 suffering from dermatitis) were patch-tested (48-hr covered contact) with 1% 3-hydroxy-2-naphthoic acid in petrolatum (Kozuka et al., 1980). Due to the small number of subjects, no final assessemant regarding the sensitising potential of 3-hydroxy-2-naphthoic acid in humans can be drawn from this study.

Conclusion

3-Hydroxy-2-naphthoic acid has a skin sensitisation potential. 3-Hydroxy-2-naphthoic acid (1% in acetone) was a sensitiser in a guinea pig maximization test after open epicutaneous challenge. Patch-tests in 36 humans gave no indication of a sensitising effect, however no conclusions can be drawn from these limited studies in humans regarding the skin sensitisation potential of 3 hydroxy-2-napthoic acid.

3.1.5 Repeated Dose Toxicity

In a 28 day gavage study in Wistar rats (0, 12, 60, 300 mg/kg bw/day), performed in accordance with the old OECD TG 407 (1981), 3-hydroxy-2-naphthoic acid had no influence on body weights, food consumption and behaviour of the animals. In the high-dose group, an increased water consumption was observed during the first two study weeks; at the end of the study, the serum phosphate levels were significantly decreased and bilirubin levels were increased in serum and urine in both sexes. Females showed a slight, but statistically significant increase in liver weights at 300 mg/kg bw/day (without histopathological correlate)(no further details available). At histopathology, one female of the high-dose and one female of the mid-dose group showed adrenal necroses. NOEL: 60 mg/kg bw/day (males), 12 mg/kg bw/day (females) (Hoechst AG, 1989a). Poorly documented studies in rats involving repeated administration by the inhalation route gave indications of an effect on the kidneys (kidney necroses were reported after 10-days inhalation of 100 mg/m3)(Prosolenko NV and Vasilenko NM, 1979).

Conclusion

After repeated administration to rats by the oral route for 28 days, there were indications of a possible effect on the adrenals in females at dose levels of 60 mg/kg bw/day and above. The only effects observed in males were a significantly reduced serum phosphate level and increased levels of bilirubin in serum and urine at a dose level of 300 mg/kg bw/day. The same findings, and, in addition, increased liver weights were reported for females at 300 mg/kg bw/day. NOEL (male): 60 mg/kg bw/day; NOEL (female): 12 mg/kg bw/day.

Poorly documented studies in rats involving repeated administration by the inhalation route gave indications of an effect on the kidneys (kidney necroses were reported after 10-days inhalation of 100 mg/m3)

3.1.6 Mutagenicity

In vitro Studies

3-Hydroxy-2-naphthoic acid was judged to be nonmutagenic in three Ames-tests using Salmonella typhimurium strains and Escherichia coli WP2uvrA, both in the presence and in the absence of metabolic activation (liver S-9 mix) (Shimizu et al., 1985; Hoechst AG, 1982; JETOC, 1996). However, the data presented in one source (JETOC, 1996) give a hint of possible, very weak activity in two strains (TA1537 and TA1538) only in the absence of S9, and in another study (Hoechst AG, 1982), some evidence of an effect was seen in strain TA1537, again in the absence of S9, although no such activity was detected in a re-test.

In a GLP study performed according to OECD TG 473, 3-hydroxy-2-naphthoic acid induced chromosome aberrations in Chinese hamster cells 6 and 18 hours after treatment with the highest test concentration (750 ug/mL) in the absence of metabolic activation. The number of chromosome aberrations was substantially greater than the increase induced by the positive control. No clastogenic effect was noted in the presence of metabolic activation. A significant cytotoxic effect was not observed (Hoechst AG, 1989b).

In vivo Studies

In vivo, 3-hydroxy-2-naphthoic acid (suspended in starch mucilage) did not induce chromosome aberrations in Chinese hamsters orally exposed to 2000 mg/kg bw. The GLP study was generally performed in accordance with OECD TG 475, however only 50 metaphases per animal were scored for chromosomal aberrations (Hoechst AG, 1993). No clinical signs of toxicity were observed, and there was also no reduction of the mitotic index in bone marrow cells, indicating that the test substance was not cytotoxic.

Conclusion

3-Hydroxy-2-naphthoic acid was judged non-mutagenic in three Ames tests, but caused chromosomal damage in V79 hamster cells in vitro (only in the absence, but not in the presence of metabolic activation). No clastogenic activity, and no toxicity was observed in vivo in bone marrow cells of hamsters, dosed with the maximum recommended dose of 2000 mg/kg bw, suspended in starch mucilage. Due to severe limitations (only 50 metaphases were examined per animal and there was no indication that the target tissue was reached by the chemical), the available in vivo study is not sufficient to assess whether the in vitro mutagenic activity is reproduced in vivo.

3.1.7 Carcinogenicity

No data available.

3.1.8 Toxicity for Reproduction

Effects on Fertility and Developmental Toxicity

In a one-generation study in Sprague-Dawley rats, performed in accordance with OECD TG 415 (Environmental Health Bureau, 2000), males were dosed with 3-hydroxy-2-naphthoic acid (purity 99.2%) by gavage for 10 weeks prior to mating, during the mating period and until the day before necropsy (in total, 98 days) and females for 2 weeks prior to mating, during mating and gestation and until day 20 of lactation (0; 12.5; 50; 200 mg/kg bw/day). The administration of the test substance had no effect on reproductive performance. No adverse effect of the test substance was observed on pairing days until conception and number of vaginal estrous during the mating period. Furthermore, no abnormality was found in delivery and nursing conditions, and no adverse effects of the test substance on gestation index and gestation length were found (No Effect Level (NOEL) for reproductive toxicity: 200 mg/kg bw/day).

After dosing, 200 mg/kg bw/day caused transient salivation in both sexes and nasal discharge in males. Body weight gain was significantly reduced in both sexes.

12.5 and 50 mg/kg bw/day had no effects on general condition, body weight gain and food consumption. At necropsy, thickening of the mucosa of the forestomach was observed in some animals of the high-dose group. Histopathological examination revealed hyperplasia of the forestomach squamous epithelium in the male animals of the mid- and high-dose groups and in females of the high-dose group. Three male animals of the high dose group showed enlarged livers without histopathological changes. No histopathological changes were found in bone marrow, spleen, adrenals, pituitary glands, testes, epididymides, coagulating glands, seminal vesicles, prostates, ovaries, uterus, cervix and vagina. 12.5 mg/kg bw/day caused neither macroscopic nor microscopic changes. The NOEL for systemic toxicity was 12.5 mg/kg bw/day in males, and 50 mg/kg bw/day in females.

Administration of the test substance did not affect viability and general condition, including behaviour of the offpring. There was no effect on the number of stillbirth, number of live pups, delivery index, birth index, sex ratio, viability index and weaning index. Decreased body weights were found in the pups of both sexes in the high-dose group from birth (-15% vs control), until day 21 (-9%). The NOEL for toxicity to the offspring was 50mg/kg bw/day.

There was an increase in the incidence of offspring with external malformations, such as kinked tail (n=1), brachyury (5), brachyury with kink (1) or microphthalmus (1, dead offspring) in the high-dose group (offspring from 2 out of 25 dams; no pup in the control showed morphological changes). In addition, there were two dead offspring of two dams with visceral malformations in this group, such as undescended testes, hypoplasia of the spleen or diaphragmatic hernia. Although all these malformations were found only in offspring of few limited litters, teratogenicity of the compound could not be ruled out from the present results according to the authors of the study. The NOEL for teratogenicity was 50 mg/kg bw/day.

Conclusion

3-Hydroxy-2-naphtoic acid was tested for its reprotoxicity in a one-generation study according to OECD TG 415. The administration of the test substance had no adverse effect on the reproductive abilities of the parental generation. Teratogenicity was observed in the offspring of few litters at maternally toxic doses. No Effect Level (NOEL) for reproductive toxicity: 200 mg/kg bw/day (highest tested dose).

NOEL for toxicity to the offspring: 50mg/kg bw/day. Growth retardation and malformations (reduced body weights, brachyury, kinked tail) were observed at 200 mg/kg bw/day in the offspring.

The NOEL for systemic toxicity in males was 12.5 mg/kg bw/day (forestomach lesions at 50 mg/kg bw/day). The NOEL for systemic toxicity in females was 50 mg/kg bw/day (reduced body weight gain, forestomach lesions at 200 mg/kg bw/day).

3.1.9 Experience with Human Exposure

No significant health effects were observed at workplace exposures up to 1 mg/m3. However, irritation of skin and mucous membranes was reported at higher exposures (ECB, 2000). Skin disease and catarrhal infection of the upper respiratory tract were reported in a group of 42 workers exposed to 3-hydroxy-2-naphthoic acid; the investigators suggested that local irritation could have played a role in this finding (further details were not given) (Prosolenko and Vasilenko, 1979).

3.2 Initial Assessment for Human Health

The acute oral LD50 of 3-hydroxy-2-naphthoic acid in rats was 823-1040 mg/kg bw. Clinical signs included reduced activity, accelerated breathing, closure of eyes, and diarrhea. Gastro-intestinal irritation and dark or mottled livers were seen in the animals that had died during the studies.

A 10% solutions of 3-hydroxy-2-naphthoic acid (approximately 2000 mg/kg bw) was lethal to guinea pigs when applied dermally for 24 hours under occlusive conditions.

Moistened 3-Hydroxy-2-naphthoic acid was slightly irritating to the skin of rabbits in a test performed according to OECD TG 404. Skin necroses and subcutaneous hemorrhages were observed in guinea pigs after occlusive exposures for 24 hours to the 10-12% solutions in mixtures of acetone and olive oil or corn oil. It caused serious damage to the eyes of rabbits (corneal vascularization/opacity) in tests performed in accordance with OECD TG 405. It may also have caused skin and upper respiratory tract irritation in workers.

3-Hydroxy-2-naphthoic acid has a skin sensitisation potential. 3-Hydroxy-2-naphthoic acid (1% in acetone) was a sensitiser in a guinea pig maximization test after open epicutaneous challenge. Patch-tests in 36 humans gave no indication of a sensitising effect, however no conclusions can be drawn from these limited studies in humans regarding the skin sensitisation potential of 3 hydroxy-2-napthoic acid.

After repeated administration to rats by the oral route for 28 days, there were indications of a possible effect on the adrenals in females at dose levels of 60 mg/kg bw/day and above. The only effects observed in males were a significantly reduced serum phosphate level and increased levels of bilirubin in serum and urine at a dose level of 300 mg/kg bw/day. The same findings, and, in addition, increased liver weights were reported for females at 300 mg/kg bw/day. NOEL (male): 60 mg/kg bw/day; NOEL (female): 12 mg/kg bw/day.

Poorly documented studies in rats involving repeated administration by the inhalation route gave indications of an effect on the kidneys (kidney necroses were reported after 10-days inhalation of 100 mg/m3).

3-Hydroxy-2-naphthoic acid was judged non- mutagenic in three Ames bacterial tests in Salmonella typhimurium and Escherichia coli strains, but it caused chromosomal damage in V79 hamster cells in vitro (only in the absence, but not in the presence of metabolic activation). No clastogenic activity, and no toxicity was observed in vivo in bone marrow cells of hamsters, dosed with the maximum recommended dose of 2000 mg/kg bw, suspended in starch mucilage. Due to severe

limitations (only 50 metaphases were examined per animal and there was no indication that the target tissue was reached by the chemical), the available in vivo study is not sufficient to assess whether the in vitro mutagenic activity is reproduced in vivo. 3-Hydroxy-2-naphtoic acid was tested for its reproductive toxicity in a one-generation study according to OECD TG 415. The administrtion of the test substance had no adverse effect on the reproductive abilities of the parental generation. At a dose level of 200 mg/kg bw/day, the body weight of the offspring was decreased. Growth retardation and malformations (brachyury, kinked tail) were observed in the offspring of few litters at a maternally toxic dose (200 mg/kg bw/day). No Effect Level (NOEL) for reproductive toxicity: 200 mg/kg bw/day (highest tested dose); NOEL for toxicity to the offspring: 50mg/kg bw/day. The NOEL for systemic toxicity in males was 12.5 mg/kg bw/day (forestomach lesions at 50 mg/kg bw/day). The NOEL for systemic toxicity in females was 50 mg/kg bw/day (reduced body weight gain, forestomach lesions at 200 mg/kg bw/day).

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Only a few test results with aquatic organisms are available:

a) fish

Brachydanio rerio 96h-LC_{50} = 68 mg/l

(static, measured concentration) (Hoechst, 1988a)

Oryzias latipes 48h-LC_{50} = 127 mg/l

(static, nominal concentration) (CITI, 1992)

Oryzias latipes 96h-LC_{50} > 82.2 mg/l

(semistatic, measured concentration) (MOE, Japan 2004)

b) invertebrates

Daphnia magna 24h-EC_{50} = 137 mg/l

48h-EC_{50} = 106 mg/l

(effect: immobilisation, measured concentration) (Hoechst, 1993a)

Daphnia magna 48h-EC_{50} = 32.9 mg/l

(effect: immobilisation, measured concentration) (MOE, Japan, 2004)

Daphnia magna 21d-NOEC = 10.4 mg/l

(effect: reproduction, measured concentration) (MOE, Japan, 2004)

c) algae

Pseudokirchneriella subcapitata 72h-E_rC_{50} = 65.3 mg/l

72h- E_bC_{50} = 26.1 mg/l

72h-NOEC = 6.8 mg/l

(measured concentration) (MOE, Japan, 2004)

d) microorganisms

Activated sludge 3h-EC_{20} = 500 mg/l

3h-EC_{50} = 1500 mg/l

(effect: respiration inhibition, EC_{50}-value was extrapolated from the concentration-effect-curve) (Hoechst, 1992b)

e) Derivation of PNECaqua

Long-term test for invertebrates and algae are available. The lowest effect value was a 72h-NOEC of f 6.8 mg/l for the green algae *Pseudokirchneriella subcapitata*. Using an assessment factor of 50 according to the EU Technical Guidance Documents results in a PNECaqua of 136 µg/l.

4.2 Terrestrial Effects

No effect values for terrestrial organisms are available.

4.3 Other Environmental Effects

There is only one test on *Agelaius phoeniceus* (red-winged blackbird) available: Based on food consumption over a 18h period, a LD_{50} >= 68 mg/l was estimated (Schafer et al., 1983).

4.4 Initial Assessment for the Environment

The environmental distribution of the substance cannot be estimated with a fugacity model as the available physico-chemical properties were determined for the undissociated acid and not for the dissociated form that is present under environmental relevant pH conditions. However, as both volatilisation and adsorption are not expected for the dissociated substance, it can be assumed that the hydrosphere is the main target compartment for 3-hydroxy-2-naphthoic acid.

3-Hydroxy-2-naphthoic acid is not readily biodegradable as was shown in a test according to OECD 301 C (1.3 % after 14 days). In a Zahn-Wellens test (OECD 302 B) with adapted inoculum the chemical was inherently biodegradable (85 % after 21 days). In a 42d bioaccumulation study with *Cyprinus carpio* BCF values of < 0.5 resp. < 4 were found for 3-hydroxy-2-naphthoic acid concentrations of 1 mg/l and 0.1 mg/l. Therefore, 3-hydroxy-2-naphthoic acid has no potential for bioaccumulation.

For 3-hydroxy-2-naphthoic acid there are short-term tests with fish, daphnids and algae available. In addition, a long-term test with *Daphnia magna* was performed. The following effect values were found:

Brachydanio rerio: 96h-LC_{50} = 68 mg/l, *Daphnia magna*: 48h-EC_{50} = 32.9 mg/l, *Pseudokirchneriella subcapitata*: 72h-E_rC_{50} = 65.3 mg/l, 72h-EbC50 = 26.1 mg/l, 72h-NOEC = 6.8 mg/l; *Daphnia magna*: 21d-NOEC = 10.4 mg/l.

With an assessment factor of 50 a PNECaqua of 136 µg/l was derived from the lowest available NOEC of 6.8 mg/l found for green algae.

5 RECOMMENDATIONS

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (that reports that the only known use of the chemical in 2 OECD countries is as an intermediate, and relating to an unknown fraction of the global production volume), exposure to the environment is anticipated to be low and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenario not presented by the Sponsor country.

Human Health: The chemical is a candidate for further work. 3-Hydroxy-2-naphthoic acid was a potent in vitro clastogen in an assay without metabolic activation. Due to severe limitations of the available in vivo chromosomal aberration study (only 50 metaphases were examined per animal and there was no indication that the target tissue was reached by the chemical), it is not possible to finally assess whether the in vitro mutagenic activity is reproduced in vivo. A standard in vivo test (mouse bone marrow chromosome aberration test (OECD TG 475) or an erythrocyte micronucleus test (OECD TG 474)) should therefore be performed as post-SIDS work. It is noted that the chemical is a skin irritant, can cause serious damage to the eye, is a skin sensitiser and there are indications of a teratogenic potential.

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I U C L I D

D a t a S e t

Existing Chemical	ID: 92-70-6
CAS No.	92-70-6
EINECS Name	3-hydroxy-2-naphthoic acid
EC No.	202-180-8
TSCA Name	2-Naphthalenecarboxylic acid, 3-hydroxy-
Molecular Formula	C11H8O3

Producer Related Part

Company:	BUA - TU München
Creation date:	03-MAY-2002

Substance Related Part

Company:	BUA - TU München
Creation date:	03-MAY-2002

Printing date:	23-NOV-2004
Revision date:	
Date of last Update:	**23-NOV-2004**

Number of Pages: **66**

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

1.1.1 General Substance Information

Substance type: organic
Physical status: solid
Purity: > 98.5 - % w/w

Test substance: BONS TTR
29-JUL-2002 (1)

Substance type: organic
Physical status: solid
Purity: > 99 - % w/w

Test substance: BONS TRTR
29-JUL-2002 (1)

1.1.2 Spectra

1.2 Synonyms and Tradenames

.beta.-Hydroxynaphthoic acid

29-AUG-1996

.beta.-Oxynaphthoic acid

29-AUG-1996

2-Hydroxy-3-carboxynaphthalene

29-AUG-1996

2-Hydroxy-3-naphthalenecarboxylic acid

29-AUG-1996

2-Hydroxy-3-naphthalincarbonsäure

19-JUN-1996

2-Hydroxy-3-naphthoesäure

19-JUN-1996

2-Hydroxy-3-naphthoic acid

29-AUG-1996

2-Hydroxynaphthalin-3-carbonsäure

29-JUL-2002

2-Naphthalenecarboxylic acid, 3-hydroxy- (9CI)

29-JUL-2002

2-Naphthalincarbonsäure (3-Hydroxy-2-naphthalincarbonsäure)

19-JUN-1996

2-Naphthalincarbonsäure, 3-hydroxy-

19-JUN-1996

2-NAPHTHOIC ACID, 3-HYDROXY-

29-JUL-2002

2-Naphthoic acid, 3-hydroxy- (8CI)

29-AUG-1996

2-naphthol-3-carboxylic acid

16-MAR-1994

3-Carboxy-2-naphthol

29-AUG-1996

3-Hydroxy-.beta.-naphthoic acid

29-AUG-1996

3-Hydroxy-2-naphthalenecarboxylic acid

29-AUG-1996

3-Hydroxy-2-naphthalincarbonsäure

19-JUN-1996

3-Hydroxy-2-naphthoic acid

29-AUG-1996

3-Naphthol-2-carboxylic acid

29-AUG-1996

beta-hydroxynaphthoic acid

06-JUN-2002

Beta-naphtoic acid, 3-hydroxy

29-OCT-1992

Beta-oxynaphthoic acid

29-JUL-2002

BON

03-MAY-2002

BON Acid

10-JUL-1998

BON Acid; Beta-Oxynaphthoic acid; 2-naphthol-3-carboxylic acid

14-MAY-1998

BONA

09-MAY-1994

BONS

29-OCT-1992

C.I. Developer 20

29-AUG-1996

C.I.DEVELOPER 8

09-MAY-1994

Developer 8

29-OCT-1992

Developer BON

29-AUG-1996

Entwickler ON

10-JAN-1997

Miketazol Developer ONS

29-AUG-1996

Naphthol B.O.N.

03-MAY-2002

1.3 Impurities

CAS-No: 135-19-3

EC-No: 205-182-7
EINECS-Name: 2-Hydroxynaphthalin
Contents: ca. 1 - % w/w

Test substance: 3-Hydroxy-2-naphthoic acid, technical dry (TTR); BONS TTR
29-JUL-2002 (1)

CAS-No: 135-19-3
EC-No: 205-182-7
EINECS-Name: 2-Hydroxynaphthalin
Contents: < .5 - % w/w

Test substance: 3-Hydroxy-2-naphthoic acid, technical pure dry (TRTR); BONS TRTR
29-JUL-2002 (1)

1.4 Additives

1.5 Total Quantity

1.6.1 Labelling

1.6.2 Classification

1.6.3 Packaging

1.7 Use Pattern

Remark: 3-Hydroxy-2-naphthoic acid is mainly used as intermediate for the production of dyes and pigments. Further uses are as intermediate for insecticides and pharmaceuticals.
29-JUL-2002 (2)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

1.12 Last Literature Search

Type of Search: External
Chapters covered: 5
Date of Search: 12-FEB-2002

Remark: Search for CAS numbers 92-70-6 and 14206-62-3 (salt) in TOXLINE, MEDLINE, TSCATS
09-JUN-2002

1.13 Reviews

Memo: Review

Reliability: (4) not assignable
01-MAY-2002 (3)

2.1 Melting Point

Value: = 220 degree C

Test substance: BONS TTR
Reliability: (4) not assignable
safety data sheet
Flag: Critical study for SIDS endpoint
25-JUL-2002 (4)

Value: > 400 degree C
Decomposition: yes at degree C

Remark: thermical decomposition
Test substance: BONS TTR
Reliability: (4) not assignable
safety data sheet
25-JUL-2002 (4)

2.2 Boiling Point

Value: 374.7 degree C

Remark: Value was estimated by EPIWin 3.1. As the substance decomposes in excess of 400 °C and does not boil prior to this temperature, further experimental boiling point data are not necessary.
05-AUG-2004

2.3 Density

Type: bulk density
Value: = 700 kg/m3

Test substance: BONS TTR
Reliability: (4) not assignable
safety data sheet
29-JUL-2002 (4)

2.3.1 Granulometry

2.4 Vapour Pressure

Remark: no data available; the vapor pressure of 2-hydroxynaphthalin is estimated with 0.014 hPa at 20 degree C. In regard to the additional carboxylic group of 3-hydroxy-2-naphthoic acid a vapor pressure of < 0.014 hPa at 20 degree C is to be expected.
29-JUL-2002

2.5 Partition Coefficient

log Pow: .17

Method: other (measured)

Remark: measured value for the sodium salt
Reliability: (4) not assignable
05-AUG-2004 (5)

log Pow: = 3.05

Method: other (measured)

Reliability: (4) not assignable
secondary quotation
25-JUL-2002 (6)

log Pow: = 3.4

Method: other (calculated): Leo, Hansch: Medchem Software CLOGP3, Release 3.42, PomonaCollege, Clermont CA
Year: 1986

Remark: Undissociated acid
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
29-JUL-2002 (7)

log Pow: = 3.42

Method: other (calculated): Epiwin Version 2.0, Syracuse Research Corporation, Environmental Science Center Merill Lane, Syracuse, NY 13210, 1996
Year: 1996

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
29-JUL-2002 (8)

log Pow: = 3.59

Method: other (calculated): according Leo, Hansch et al.: Chem. Rev. 71, 525
Year: 1971

Remark: Coefficient of undissociated acid
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
25-JUL-2002 (4) (9)

2.6.1 Solubility in different media

Value: = .104 g/l at 25 degree C
pKa: 2.8 at 25 degree C

Test substance: 3-hydroxy-2-naphthoic acid
Reliability: (4) not assignable

25-JUL-2002 (10) (9)

Value: ca. 2.6 g/l

Remark: Calculated from DOC; estimated from a neutralized saturated aqueous solution (24 h, 20 degree C, pH 8.5)
Test substance: 3-hydroxy-2-naphthoic acid
Reliability: (4) not assignable
25-JUL-2002 (11)

Descr.: of low solubility

28-MAY-1997 (4)

Value: 474 mg/l at 25 degree C

Remark: estimated value from log Kow with Epiwin 3.1; undissociated acid
Test substance: 3-hydroxy-2-naphthoic acid
Flag: Critical study for SIDS endpoint
08-AUG-2002

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

Value: > 400 degree C

Reliability: (4) not assignable
safety data sheet
29-JUL-2002 (4)

2.9 Flammability

Remark: flammability: 1
Reliability: (4) not assignable
safety data sheet
05-AUG-2004 (4)

2.10 Explosive Properties

05-AUG-2004

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: = .0000000000242091 cm³/(molecule * sec)
Degradation: = 50 % after 15.9 hour(s)

Method: other (calculated): Epiwin Version 2.0, Syracuse Research Corporation, Environmental Science Center Merill Lane, Syracuse, NY 13210, 1996
Year: 1996

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
29-JUL-2002 (12)

3.1.2 Stability in Water

Remark: no data available; hydrolytic degradation unlikely
08-AUG-2002

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: adsorption
Media: water - soil
Method: other: (calculated): Epiwin Version 2.0, Syracuse Research Corporation, Environmental Science Center Merill Lane, Syracuse, NY 13210, 1996
Year: 1996

Remark: as the substance is dissociated under environmental relevant pH conditions, the estimated Koc-value for the undissociated acid is not valid for environmental assessment purposes
Result: log Koc = 2.425
Reliability: (2) valid with restrictions
25-AUG-2004 (12)

Type: volatility
Media: water - air
Method: other: (berechnet): Epiwin Version 2.0, Syracuse Research Corporation, Environmental Science Center Merill Lane, Syracuse, NY 13210, 1996
Year: 1996

Remark: as the substance is dissociated under environmental relevant pH conditions, the estimated Henry constant for the undissociated acid is not valid for environmental assessment purposes
Result: Henry constant (25 °C): 1.39E-009 atm-m3/mole (calculated according to Bond SAR Methode)

volatilisation from water:
half-life from model river: 3.611E+004 Tage
half-life from model lake: 2.626E+005 Tage
Reliability: (2) valid with restrictions
08-AUG-2002 (8)

3.3.2 Distribution

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Degradation: = 1.3 % after 14 day(s)
Control Subst.: Aniline

Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
GLP: no data
Test substance: other TS

Result: not readily biodegradable
Test condition: sludge was sampled at 10 different places in Japan (e.g. city sewage plants, indurstry sewage, rivers, lake and sea); sludge concentration: 30 mg/l; cultivating temperature: 25 °C; test parameter: BOD
test duration was only 14 d
Test substance: 3-hydroxy-2-naphthoic acid
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-NOV-2004 (13)

Type: aerobic
Inoculum: activated sludge, industrial
Concentration: 300 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 85 % after 28 day(s)
Result: inherently biodegradable
Kinetic:
3 hour(s) = 0 %
5 day(s) = 0 %
10 day(s) = 23 %
15 day(s) = 70 %
21 day(s) = 85 %

Method: OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year: 1987
GLP: no
Test substance: other TS

Remark: total elimination is due to biodegradation
Result: The same elimination after 28 days was reached for the concentration 154 mg/l (related to DOC).
Test substance: 3-hydroxy-2-naphthoic acid, purity: 99 %
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
25-JUL-2002 (14)

Type: aerobic
Inoculum: activated sludge, industrial
Degradation: > 90 % after 20 day(s)
Kinetic:
3 day(s)	< 10 %
5 day(s)	< 10 %
10 day(s)	= 40 %
15 day(s)	= 70 %

Method: other: Zahn-Wellens-Test, DIN 38412, L25
Year: 1988
GLP: no
Test substance: other TS

Test condition: The test was done with a saturated solution after 24 h stirring at 20 °C; pH = 8.5; substance content about 2.6 g/l
Test substance: 3-hydroxy-2-naphthoic aci, purity: 98.5 %
Reliability: (4) not assignable
08-AUG-2002 (11)

Type: aerobic
Inoculum: activated sludge, industrial, adapted
Concentration: 240 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 3 % after 1 day(s)

Method: other: activated sludge simulation test
GLP: no data

Test condition: Fill and draw type unit, operating at 25 °C and MLVSS 400 mg/l, fed with activated sludge from an industrial wastewater treatment plant. This plant serviced several chemical manufacturers and the sludge was therefore considered to be well acclimatised to a variety of chemicals. Biodegradation was followed by determination of BOD and TOC.
Test substance: 3-hydroxy-2-naphthoic acid
Reliability: (2) valid with restrictions
23-NOV-2004 (15)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 42 day(s) at 25 degree C
Concentration: .1 mg/l
BCF: < 4
Elimination: no data

Method: other: according to OECD Guide-line 305 C "Bioaccumulation: Degree of Bioconcentration in Fish"

GLP: no data
Test substance: other TS

Result: With a concentration of 1 mg/l a BCF of < 0.5 was found.
Test condition: Weight, lenght and lipid content of test fish at begin of exposure:
weight: about 30 g
lenght: about 10 cm
lipid content: 2 - 6 %

During exposure test fish were fed twice a day with pelleted carp feed in a total amount of 2 % of the total body weight.

Test tanks: 100 l, flow rate: 200 - 800 ml/min, temperature: 25 °C, concentration of DO: 6 - 8 mg/l,
number of test fish per exposure tankL 15 - 20
Test substance: 3-Hydroxy-2-naphthoic acid
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-NOV-2004 (16)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
LC0: 40.8 -
LC50: > 82.2 -
LC100: > 82.2 -
Limit Test: no

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2004
GLP: yes
Test substance: other TS: Wako Pure Chemical Industries, Ltd., Lot. No.;WAP0402, Purity = 100%

Method: -Test Organisms:
a) Supplier: Test organisms were obtained from home-reraed fish which ovums started collecting on 5-Sep. 2004.
b) Size (length and weight): 1.79 cm (1.54 - 1.99cm) in length; 0.090 g (0.046 - 0.118 g) in weight.
c) Age: About half year after hatching.
d) Any pretreatment: Test organisms were acclimated for 31 days before testing. During acclimation, test fishes were fed with TETRAMINE(20% of fish weight). The mortality of the test organisms for 7 days before testing was below 5%. LC50(96 hr) for a reference substance (copper sulfate pentahydrate) was 0.64 mg/L.

-Test substance: 3-hydroxy-2-naphthoic acid
a) Empirical Formula: C11H8O3
b) Molecular Weight: 188.18g/mol
c) Purity: =100 %
d) Melting point: 222C
e) Water Solubility: 89.9mg/L(20C)

-Test Conditions:
a) Dilution Water Source: Dilution water was prepared from tap water (Yokohama in Japan). The tap water was dechlorinated, treated by activated carbon and aerated.
b) Dilution Water Chemistry:
pH: = 7.2 (21C)
Total hardness (as CaCO3): = 59 mg/L
c) Exposure Vessel Type: 5 L glass beaker
d) Nominal Concentrations: control, 20.0, 28.0, 40.0, 57.0 and 80.0 mg/L
e) Vehicle/Solvent and Concentrations: Not used.
f) Stock Solutions Preparations and Stability: Test substance was diluted with dilution water. Test substance was stored in freezer. The stability of the chemical was confirmed by IR absorption spectrum. Under the stock condition, IR spectrum of the test substance at the end of test was same at the start.

g) Number of Replicate: 1
h) Fish per Replicates: 10
i) Renewal Rate of Test Water: All water replaced after 48 hours.
j) Water Temperature: 24+/1C

k) Light Condition: 16:8 hours, light-darkness cycle
l) Feeding: None
m) Aeration : Done.

-Analytical Procedure:
The test concentrations were measured at the start of exposure and before the water relracement using HPLC.-Statistical Method:
a) Data Analysis: LC50 and 95% confidence intervals were calculated by proper method selected in three methods, Binomial method, Moving average method, Pobit method .
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Geometric mean.

Result: - Measured Concentrations: The test concentrations were measured at the start of exposure and before the water replacement.

Nominal Conc. mg/L new	Measured Conc. mg/L (Percent of Nominal) 0 Hour old	48 Hour mean	Geometric
Control	<0.002	<0.002	
20.0	21.1 (106)	20.5 (101)	20.8 (104)
28.0	29.4 (105)	29.0 (104)	29.2 (104)
40.0	40.9 (102)	40.7 (102)	40.8 (102)
57.0	59.0 (104)	57.5 (101)	58.2 (102)
80.0	83.3 (104)	81.2 (102)	82.2 (103)

new: freshly prepared test solutions
old: test solutions after 48 hours exposure

- Water chemistry (pH and DO and temperature in test): Water chemistry and temperature were measured for each concentration at the start of test, once or more a day and before and after water replacement.
pH: 6.0 - 8.5
DO: 7.4 - 8.4 mg/L
Water Temperature: 23.6 - 24.9C

-Effect Data(mortality):
LC50 (96hr) > 82.2 mg/L (mc) (95%C.I.:Cannot calculated)
LC0 (96hr) = 40.8 mg/L (mc)
LC100 (96hr) > 82.2 mg/L (mc)
mc: based on Geometric mean of measured concentration

- Cumulative Mortality: The lowest concentration from which the test organisms were killed was 57.0 mg/L after 96 hour (except for the control).

Measured Conc. mg/L	Cumulative Number of Dead (Percent Mortality) 24 Hour	48 Hour	72 Hour	96 Hour
Control	0 (0)	0 (0)	0 (0)	1 (10)
20.8	0 (0)	0 (0)	0 (0)	0 (0)
29.2	0 (0)	0 (0)	0 (0)	0 (0)
40.8	0 (0)	0 (0)	0 (0)	0 (0)
58.2	0 (0)	0 (0)	0 (0)	1 (10)

82.2 3 (30) 3 (30) 3 (30) 3 (30)

-Other Effect: Symptoms of toxicity were observed: abnormal swimming (reduced activity: 82.2mg/L).

Measured Conc. mg/L	Symptoms 24 Hour	48 Hour	72 Hour	96 Hour
Control	N	N	N	N
20.8	N	N	N	N
29.2	N	N	N	N
40.8	N	N	N	N
58.2	N	N	N	N
82.2	ASR-2	ASR-1	ASR-1	N

: No toxicological symptom was observed.
ASR : Abnormal swimming (reduced activity)

- Calculation of toxicity values: The calculation of toxicity values was the Geometric mean of measured concentration.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-AUG-2004 (17)

Type: static
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
LC0: = 50 -
LC50: 68 -
LC100: = 100 -

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 1988
GLP: yes
Test substance: other TS

Remark: At the concentration of 10 mg/l after 24 h exposition of an increasing of activity was observed. At 50 to 71 mg/l the fishes shows symptoms of intoxication, as sticking out of gill cover, increasing respirationrate, erratic swimming loss of equlibrium, decreasing activity and increasing of frightreaction. At 50 mg/l these symptoms has been observed only in the first 24 h. All fishes in the 100 mg/l group died in the first 24 h.
Test condition: pH: 7.5 - 8.2; T: 21.1-22.9 degree C; DO: 7.1-9.2 mg/l
Test substance: 3-hydroxy-2-naphthoic acid; purity: 98.5 %
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
05-AUG-2004 (18)

Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
LC50: = 127 -

Test condition: static or semistatic (renewal of test water at every 8 - 16 hours)

Test substance: 3-hydroxy-2-naphthoic acid
Reliability: (2) valid with restrictions
08-AUG-2002 (13)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** yes
EC0: = 56 -
EC50: = 137.03 -

Method: OECD Guide-line 202
Year: 1992
GLP: yes
Test substance: other TS

Test condition: pH: 8.2-8.9; T: 20.4-21.9 degree ; DO: 7.1-8.7 mg/l
Test substance: Beta-Oxynaphtoesäure (BONS) TRTR; purity: 97.9 %
Reliability: (1) valid without restriction
25-JUL-2002 (19)

Type: semistatic
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
EC0: 14.7 -
EC50: 32.9 -
EC100: 46.7 -
Limit Test: no

Method: OECD Guide-line 202
Year: 2004
GLP: yes
Test substance: other TS:Wako Pure Chemical Industries, Ltd., Lot. No.;WAP0402, Purity = 100%

Method: -Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: Test organisms were obtained from the National Institute of Environmental Studies(JAPAN).
c) Any pretreatment: Parental daphnids were acclimated for 20 days on test condition before testing. During acclimatization, test daphnids were fed with Chlorella vulgaris, 0.2 mg carbon/day/individual. During 2 weeks before acute toxicity test, mortality of the test daphnia was below 5% and any resting-egg and male daphnia were not observed. EC50 (48hr, immobility) for reference substance (potassium dichromate) was 0.76mg/L.

-Test substance: 3-hydroxy-2-naphthoic acid
a) Empirical Formula: C11H8O3
b) Molecular Weight: 188.18g/mol
c) Purity: =100 %
d) Melting point: 222C
e) Water Solubility: 89.9mg/L(20C)

-Test Conditions:
a) Dilution Water Source: Elendt M4 medium was used as

dilution water.
b) Dilution Water Chemistry:
c) Exposure Vessel Type: 100 mL test solution in a 100 mL glass beaker with cap. Surface of test solution was coverd with teflon sheet.
d) Nominal Concentrations: control, 8.00, 14.0, 25.0, 45.0 and 80.0mg/L
e) Vehicle/Solvent and Concentrations: Not used.
f) Stock Solutions Preparations and Stability: Stock solution was prepared by mixing test substance with Elendt M4 medium using ultrasonic wave (30 minutes) with stopper. Test substance was stored in freezer. The stability of the chemical was confirmed by IR absorption spectrum. Under the stock condition, IR spectrum of the test substance at the end of test was same at the start.
g) Number of Replicates: 4
h) Individuals per Replicates: 5
i) Water Temperature: 20+/-1C
j) Light Condition: 16:8 hours, light-darkness cycle (<800 lux)
k) Feeding: None
l) Aeration : Test solution was not aerated during the test period

- Analytical Procedure: Test concentrations were measured at the start and the end of test using HPLC.

- Statistical Method:
a) Data Analysis: EC50 and 95% confidence intervals were calculated by Binomial method.
b) Method of Calculating Mean Measured Concentrations: Geometric mean.

Result: - Measured Concentrations: The test concentrations were measured at the start and 48th hour during test period.

Nominal Conc.	Measured Conc. [mg/L]			Percent of Nominal [%]	
mg/L	0 Hour	48 Hour	Geometric	0 Hour	48 Hour
Fresh	Old	Mean	Fresh	Old	
Control	<0.002	<0.002	---	---	---
8.00	8.44	8.24	8.34	106	103
14.0	14.9	14.5	14.7	106	104
25.0	26.6	26.1	26.3	106	104
45.0	47.1	46.3	46.7	105	103
80.0	85.9	81.7	83.8	107	102

Fresh: freshly prepared test solution.
Old : test solutions after 48 hours exposure

- Water chemistry (pH and DO and temperature in test): Water chemistry and temperature were measured for control and each concentration at the start and before the water replacement.
pH: 6.5 - 8.5
DO: 8.5 - 8.8 mg/L
Water Temperature: 19.9 - 20.3C
Total Hardness(as CaCO3): 240 - 250 mg/L

-Effect Data:
EC50 (48hr) = 32.9 mg/L (mc) (95%C.I.: 26.3 - 46.7 mg/L)

EC100 (48hr) = 46.7 mg/L (mc)
NOEC (48hr) = 14.7 mg/L (mc)
mc: based on geometric mean of measured concentration.

-Mortality or Immobility: None of test organisms in the control were immobilized. The lowest concentration at which the test organisms were immobilized was 26.3 mg/L at 48 hours.

Measured Conc. mg/L	Cumulative Number of Immobilized Daphnia (Percent Immobility) 24 Hour	48 Hour
Control	0 (0)	0 (0)
8.34	0 (0)	0 (0)
14.7	0 (0)	0 (0)
26.3	0 (0)	2 (10)
46.7	20 (100)	20 (100)
83.8	20 (100)	20 (100)

- Calculation of toxic values: Geometric mean of measured concentration.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-AUG-2004 (17)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
EC0: = 56 -
EC50: 106 -
EC100: = 180 -

Method: OECD Guide-line 202
Year: 1992
GLP: yes
Test substance: other TS

Test condition: H: 8.2-8.9; T: 20.4-21.9 degree ; DO: 7.1-8.7 mg/l
Test substance: Beta-Oxynaphtoesäure (BONS) TRTR; Reinheit: 97.9 %
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
05-AUG-2004 (19)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Agmenellum quadruplicatum (Algae)
Endpoint: growth rate

Method: other: Algal lawn bioassay
GLP: no
Test substance: no data

Remark: No growth inhibition was observed up to concentration of 2 mg/disc. At concentrations of 5 mg/disc a slight inhibition was seen (2 in a scale of 0 - 36).
Test condition: The stock solution of the compound were made in water or 95 % ethanol. The test materials were absorbed on water washed cellulose discs and placed in the center of the petridishes and incubated at 30 - 34 °C. The zones of inhi-

bition were examined visually and microscopically after 5 to 10 days.
Test substance: 3-hydroxy-2-naphthoic acid
Reliability: (3) invalid
05-AUG-2004 (20)

Species: other algae: Pseudokirchneriella subcapitata
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: 6.8 -
EC50: 65.3 -

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2004
GLP: yes
Test substance: other TS

Method: - Test organisms:
a) supplier/source: Obtained from American Type Culture Collection
b) Method of cultivation: sterile
c) Strain number: ATCC22662
d) Any pretreatment: Acclimated for 5 days before testing.

- Test substance: 3-hydroxy-2-naphthoic acid
a) Empirical formula: C11H8O3
b) Molecular weight: 188.8 g/mol
c) Purity: 100 %

- Test conditions:
a) Medium: OECD medium
b) Exposure vessel type:100 ml medium in a 300 ml glass Erlenmeyer flask with silikon breathable cap
c) Nominal concentrations: control, 2.00, 3.7, 6.8, 13, 23, 43 and 80 mg/l
d) Vehicle/Solvent and Concentrations: not used
e) Stock solution: 3-hydroxy-2-naphthoic acid was diluted with OECD medium
f) Number of replicates: 3
g) Initial cell number: 10,000 cells/ml
h) Water temperature: 23 +/- 2 °C
i) Light conditions: 4,000 lux (fluctuation within +/-20 %), continuously
j) Shaking: 100 rpm

- Anayltical procedure: Test concentrations were measured at the start and after 72 hours.

- Statistical method:
a) Data analysis: Linear regression analysis (least-square method) for EC50. 1-way ANOVA (a = 0.05) and Dunett's method (a=0.05, both sides) for NOEC, after Bartlett's homoscedastic test.
b)Method of calculating mean measured concentrations (i.e. arithmetic mean, geometric mean): not described.
Remark: NOEC was determined based on growth inhibition
Result: - Measured concentrations: The tested concentrations were measured at the start and after 72 hours. For all of them, the deviation from the nominal concentrations were less than +/- 10 %.

Nominal	Measured Conc., mg/L		Percent of nominal Conc.	
mg/L	0 Hour	72 Hour	0 Hour	72 Hour
Fresh	Old	Fresh	Old	
Control	<0.002	<0.002	---	---
2.00	2.11	1.99	106	100
3.70	3.91	3.68	106	99
6.80	7.21	6.71	106	99
13.0	13.6	12.8	105	98
23.0	23.5	22.6	102	98
43.0	44.5	42.7	103	99
80.0	83.0	78.9	104	99

Fresh: freshly prepared test solution
Old: test solution after 72 hours exposure

- Water chemistry (pH) and temperature in test: pH was measured for control and each concentration at the start and end of the test. At the start pH was 6.3 - 7.9 and at test end pH was 7.4 - 10.0. Temperature: 23 +/- 2 °C

Nominal Concentration.	pH	
mg/L	0 Hour	72 Hour
Control	7.9	9.4
2.00	7.8	9.3
3.70	7.7	10.0
6.80	7.6	9.7
13.0	7.4	9.3
23.0	7.4	9.0
43.0	6.9	7.8
80.0	6.3	7.4

At the end of the test pH increased by more than 1 unit compared with the test start in all treatments except for the control and the concentration 43 mg/l. When carbon dioxide assimilation is active and growth rate is high, pH often increases by more than 1 unit.

- Effect data: Area method
EbC50 (0-72 h) = 26.1 mg/l (95% C.I.: 21.6 - 31.6 mg/l)
NOEC (0-72 h) = 6.8 mg/l

Rate method:
ErC50 (0-72 h) = 65.3 mg/l (95% C.I.: 57.6 - 75.9 mg/l)
NOEC (0-72 h) = 6.8 mg/l

These toxic values were calculated based on the nominal concentrations because the analytical measurement showed this chemical was stable under the test conditions and the deviations from the nominal value was not more than 10 %.

- Growth Inhibition (%) of Pseudokirchneriella subcapitata

Nominal Conc.	Area under the growth curves (Average)	
	Area	Inhibition (%)

mg/L	A (0-72hr)	IA (0-72hr)
Control	49,475,000	---
2.00	54,165,000	-9.5
3.70	45,859,000	7.3
6.80	44,916,000	9.2
13.0	36,973,000	25.3**
23.0	28,732,000	41.9**
43.0	12,860,000	74.0**
80.0	1,598,000	96.8++

+ Statistical comparison test was performed excepting this concentration since when the data including this concentration did not show homogeneity of variances.

Growth rates (Average) and inhibition (%)

Nominal Conc. mg/L	Rate μ(0-72hr)	Inhibition(%) Iμ(0-72hr)
Control	0.0795	---
2.00	0.0807	-1.51
3.70	0.0780	1.97
6.80	0.0775	2.53
13.0	0.0744	6.47**
23.0	0.0707	11.1**
43.0	0.0596	25.0**
80.0	0.0240	69.9**

Growth Curves: Exponetial grwoth phase was observed throughout the test preiod except in the highest concentration.

- Calculation of toxic value: It was the measured concentrations at the start
** indicates a significant difference (a = 0.01) from the control.

Test substance: Wako Pure Chemical Industries Ltd., Lot No.: WAP0402, purity: 100 %
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
26-AUG-2004 (17)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge, domestic
Exposure period: 3 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: ca. 1500 -
EC20 : ca. 500 -

Method: OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year: 1988
GLP: no
Test substance: other TS

Test substance: BONS TTR, purity: 98.5 %
Flag: Critical study for SIDS endpoint

08-AUG-2002 (11)

Type: aquatic
Species: anaerobic bact. from a domestic water treatment plant
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC20 : = 1250 -

Method: ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"
Year: 1987
GLP: no
Test substance: other TS

Test condition: temperature: 37 degree C
Test substance: BONS TTR, purity: 99 %
08-AUG-2002 (21)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: 10.4 -
LOEC: 33.1 -
EC50: 24 -

Method: OECD Guide-line 211
Year: 2004
GLP: yes
Test substance: other TS: Wako Pure Chemical Industries, Ltd., Lot. No.;WAP0402, Purity = 100%

Method: -Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: Test organisms were obtained from the National Institute of Environmental Studies (JAPAN).
c) Any pretreatment: Parental daphnids were acclimated for 28 days on test condition before testing. During acclimatization, test daphnids were fed with Chlorella vulgaris, 0.2 mg carbon/day/individual. During 2 weeks before acute toxicity test, mortality of the test daphnia was 0 % and any resting-egg and male daphnia were not observed. EC50 (48hr, immobility) for reference substance (potassium dichromate) was 0.76mg/L.

-Test substance: 3-hydroxy-2-naphthoic acid
a) Empirical Formula: C11H8O3
b) Molecular Weight: 188.18g/mol
c) Purity: =100 %
d) Melting point: 222C
e) Water Solubility: 89.9mg/L(20C)

-Test Conditions:
a) Dilution Water Source: Elendt M4 medium was used as dilution water.
b) Dilution Water Chemistry:
c) Exposure Vessel Type: 80 mL test solution in a 100 mL glass beaker with cap. Surface of test solutions were covered with teflon sheet.
d) Nominal Concentrations: control, 0.320, 1.00, 3.20, 10.0 and 32.0 mg/L
e) Vehicle/Solvent and Concentrations: Not used.
f) Stock Solutions Preparations and Stability: Stock solution was prepared by mixing test substance with Elendt M4 medium using ultrasonic wave (30minetes) with stopper. The Stock solution was prepared every 1-4 days and stored under dark condition in freezer. Test substance was also stored in freezer. The stability of the chemical was confirmed by IR absorption spectrum. Under the stock condition, IR spectrum of the test substance at the end of test was same at the start.

g) Number of Replicates: 10
h) Individuals per Replicates: 1
i) Water Temperature: 20+/-1C
j) Light Condition: 16:8 hours, light-darkness cycle
k) Feeding: 0.15 mg carbon/day/individual (Chlorella vulgaris: Green Algae)
l) Aeration : None

- Analytical Procedure: The test concentrations were measured three times during test period using HPLC.

- Statistical Method:
a) Data Analysis: LC50 and EC50: LC50 and their 95%c.l. were calculated by Probit method. EC50 and 95% C.I. were calculated by Logit method. Both LC50 and EC50 was calculated using the concentrations of 0.313 - 33.1 mg/L.
NOEC and LOEC: The cumulative number of juveniles produced per adult in control and test concentration after 21days was tested by Kruskal-Wallis test and nonparametric Dunnett test after Bartlett's homoscedastic test (Yukms Co. Ltd. Statlight #4).
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Time-weighted Mean

Result: - Effect: reproduction

- Measured Concentrations: The test concentrations were measured for both fresh and old test solution at three times during test period.

Nominal Conc. mg/L	Date	Measured Concentration [mg/L] 0		1		9		10		16		17
		Fresh	Old	Fresh	Old	Fresh	Old					
Control		<0.002		<0.002		<0.002		<0.002		<0.002		<0.002
0.320		0.333		0.309		0.328		0.314		0.296		0.297
1.00		1.06		1.04		1.05		1.03		1.01		1.01
3.20		3.40		3.36		3.44		3.33		3.36		3.37
10.0		10.4		10.4		10.5		10.5		10.2		10.3
32.0		33.7		33.3		33.9		32.2		32.9		32.6

Fresh: freshly prepared test solution.

Old : old test solutions before renewal

Nominal Conc. mg/L	Time-weighted mean mg/L	Percentage of nominal %
Control	---	---
0.320	0.313	98
1.00	1.03	103
3.20	3.38	106
10.0	10.4	104
32.0	33.1	103

Fresh: freshly prepared test solution.
Old: old test solutions before renewal

- Water chemistry (pH, DO and and temperature in test): Water chemistry and temperature were measured for control and each concentration at the start of test and before and after water replacement (4 times) during exposure.
pH: 7.3 - 8.4
DO: 7.2 - 8.8 mg/L
Water Temperature: 19.9 - 20.5C
Total Hardness (as CaCO3): 242 - 248 mg/L

-Effect Data (Reproduction):
LC50 (21days) = 16.5 mg/L (parental mortality) (mc)
(95%C.I.: 10.6 - 26.3 mg/L)
EC50 (21days) = 24.0 mg/L (mc)
(95%C.I.: Cannot be calculated)
NOEC (21days) = 10.4 mg/L (mc)
LOEC (21days) = 33.1 mg/L (mc)
mc: based on Time-weighted mean of measured concentrations

- Cumulative Number of Died Parental Daphnia:. Mortality rate of parental Daphnia at the control was 0 %.

Measured Conc. (mg/L)	Cumulative Number of Dead Parental Daphnia After 21days
Control	0 (0)
0.313	0 (0)
1.03	0 (0)
3.38	0 (0)
10.4	2 (20)
33.1	9 (90)

-Cumulative numbers of juveniles produced per adult : No juveniles were produced by test organisms at highest concentration.

Measured Conc. mg/L	Mean Cumulative Numbers of Juveniles Produced per Adult for 21 days
Control	104.9
0.313	120.0
1.03	120.9
3.38	112.2
10.4	124.0
33.1	25.0

Vessel No.	Measured Concentration [mg/L]					
Control	0.313	1.03	3.38	10.4	32.0	
1	84	112	103	115	125	D
2	109	133	125	109	103	D
3	102	106	129	119	139	D
4	93	120	118	117	129	25
5	92	120	128	114	D	D
6	107	126	106	99	120	D
7	117	112	134	105	D	D
8	110	138	115	127	121	D
9	125	124	136	105	121	D
10	110	109	115	112	134	D
Mean	104.9	120.0	120.9	112.2	124.0	25.0
S.D.	12.4	10.5	11.3	8.1	10.9	
Inhibition rate(%)		-14.4	-15.3	-7.0	-18.2	76.2
Significant difference		*,S	**,S	---	**,S	++

D : Were not included for calculation because the parental Daphnia was dead during a 21-day testing period.
- : Indicates no significant difference.
*,** : Indicates a significant difference (a=0.05, 0.01) from the control.
S : Mean cumulative number for this concentration level was higher than that for control group. We concluded that this concentration level did not show adverse effect on Daphnia reproduction. As the test substance was not degraded during exposure, the growth of bacteria being nutrition for Daphnia seemed not to occur.
++ : Statistical comparison test could not be performed for this concentration. However, we concluded that this concentration level showed adverse effect on Daphnia reproduction.

-Calculation of toxicity values: The calculation of toxicity values was the time weighted mean of measured concentrations.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-AUG-2004 (17)

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Species: other avian: Agelaius phoeniceus (Redwinged blackbird)
Endpoint: mortality
Expos. period: 18 hour(s)
Unit: mg/kg bw
LD50 : = 68 -

GLP: no data

Remark: Estimated LD50 based on food consumption data over a 18 h period.
Test substance: 3-hydroxy-2-naphthoic aci
Reliability: (2) valid with restrictions
08-AUG-2002 (22)

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo: In vivo
Species: guinea pig
Route of administration: dermal

Method: other
Year: 1958
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid; purity not stated

Method: The 12% solution of the test substance in a mixture of acetone and olive oil was held in contact with the depilated skin of guinea pigs for twenty-four hours. Dose level not stated. Number of animals not stated.
Result: There was evidence of dermal absorption since a guinea pig died within twenty-four hours after dermal application of the test substance (the skin was edematous, necrotic and there was some subcutaneous hemorrhage).
Reliability: (4) not assignable
no experimental details available.
Flag: Critical study for SIDS endpoint
09-JUN-2002 (23)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Wistar
Sex: male/female
No. of Animals: 10
Vehicle: other: 2% aqueous carboxymethylcellulose
Doses: 315; 500; 800; 1000; 1250 mg/kg bw
Value: = 823 mg/kg bw

Method: OECD Guide-line 401 "Acute Oral Toxicity"
Year: 1983
GLP: yes
Test substance: other TS: BONS TTR, impurity: ca 1% 2-naphthol

Method: 5 animals per sex per dose (only 5 females each were used at the two lowest doses). Fasted animals (food withdrawn 16 hours before application). The test substance was applied as a 25% preparation in 2% aqueous carboxymethylcellulose. Post-exposure observation period: 14 days.
Statistics: Probit analysis.
Result: LD50 (m/f): 823 mg/kg bw (95% confidence limits: 581-1070 mg/kg bw).
LD50 (m): 869 mg/kg bw (95% confidence limits: 394-1350 mg/kg bw).
LD50 (f): 795 mg/kg bw (95% confidence limits: 485-1320 mg/kg bw).

Mortality:
315 mg/kg: 0/5 (f)

500 mg/kg: 2/5 (f)
800 mg/kg: 1/5 (m), 2/5 (f)
1000 mg/kg: 3/5 (m), 3/5 (f)
1250 mg/kg: 5/5 (m), 4/5 (f)
Mortality occurred within 35-200 minutes after exposure.

Clinical Signs:
315, 500, 800 mg/kg bw: 10-30 minutes after application reduced activity, prostrate and lateral positioning.
1000, 1250 mg/kg bw: reduced activity, prostrate and lateral positioning, accelerated breathing and closure of eyes.
These signs were observed until the end of the day of application.
Diarrhea was seen in all groups, beginning at 30 to 60 minutes after application.
There was no influence on body weight gain.
All surviving animals were free of symptoms on day 1 after application.

At necropsy, dark coloration of the liver was found in the high dose animals that had died, whereas light-coloured spots were seen in the livers of animals that died in the 500 and 800 mg/kg bw groups.
Hyperemia and fluid were seen in the gastro-intestinal tracts. Animals that were killed at the end of the observation period were free of pathological changes.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (24)

Type: LD50
Species: rat
Strain: Wistar
Sex: male/female
No. of Animals: 10
Vehicle: other: 2% aqueous carboxymethylcellulose
Doses: 315; 500; 630; 800; 1000; 1250 mg/kg bw
Value: = 1040 mg/kg bw

Method: OECD Guide-line 401 "Acute Oral Toxicity"
Year: 1983
GLP: yes
Test substance: other TS: technical product, impurity: ca 0.6% 2-naphthol

Method: 5 animals per sex per dose (only 5 females each were used at the two lowest doses, and only 5 males were used at the dose level of 630 mg/kg bw). Fasted animals (food withdrawn 16 hours before application). The test substance was applied as a 25% preparation in 2% aqueous carboxymethylcellulose.
Post-exposure observation period: 14 days.
Statistics: Probit analysis.

Result: LD50 (m/f): 1040 mg/kg bw (95% confidence limits: 901-1290 mg/kg bw).
LD50 (m): 947 mg/kg bw (95% confidence limits: 615-1730 mg/kg bw).
LD50 (f): 1080 mg/kg bw (95% confidence limits: 754-2710 mg/kg bw).

Mortality:
315 mg/kg: 0/5 (f)
500 mg/kg: 0/5 (f)

630 mg/kg: 2/5 (m)
800 mg/kg: 2/5 (m), 0/5 (f)
1000 mg/kg: 2/5 (m), 3/5 (f)
1250 mg/kg: 3/5 (m), 4/5 (f)
Mortality occurred between 60 minutes and 1 day after exposure.

Clinical signs were similar in both sexes and included: prostrate and lateral positioning (starting at 10 minutes after administration of test substance; dose levels not specified in report), reduced activity, accelerated breathing and closure of eyes, diarrhea (starting at 30 minutes after administration, dose levels not specified) All surviving animals were free of symptoms on day 1 after application. There was no influence on body weight gain.

At necropsy, hyperemia and discoloration of the gastro-intestinal tract was seen in the animals that had died. Animals that were killed at the end of the observation period were free of pathological changes.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (25)

Type: LD50
Species: rat
Value: = 2450 mg/kg bw

Reliability: (4) not assignable
secondary citation
07-JUN-2002 (26) (27)

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: other: suspended in agar
Doses: no data
Value: = 1500 mg/kg bw

Method: other: no data
Year: 1958
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid, "undiluted", purity not stated

Reliability: (4) not assignable
data submitted to Eastman Kodak in a letter dated May 27, 1958 by Heyden Newport Chemical Corporation. No further information on methodology available.
06-JUN-2002 (28)

Type: LDLo
Species: rat
Strain: no data
Sex: no data
Vehicle: other: mixture of propylene glycol and ethylalcohol
Doses: 800 mg/kg as an 8.7% solution in the vehicle
Value: = 800 mg/kg bw

Method: other
Year: 1958
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid, "diluted", purity not stated

Result: Symptoms included ataxia and rapid respiration. Deaths were not delayed.
Reliability: (4) not assignable
Short summary. No further details on methodology available.
07-JUN-2002 (23)

Type: other: approx. LD50
Species: rat
Strain: no data
Sex: male
Vehicle: other: corn oil
Doses: 200 - 3200 mg/kg bw (not further specified) as a 10% suspension in the vehicle
Value: = 800 - 1600 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: 3-Hydroxy-2-naphthoic acid, purity not stated

Method: 5 male rats in total.
Result: Symptoms included weakness, ataxia, unconsciousness.
Reliability: (4) not assignable
Short summary. No further details available.
06-JUN-2002 (29)

Type: LD50
Species: mouse
Value: = 2700 mg/kg bw

Reliability: (4) not assignable
secondary citation
07-JUN-2002 (26) (27)

Type: LD50
Species: mouse
Value: = 800 mg/kg bw

Method: other
GLP: no data
Test substance: no data

Source: Hoechst AG Frankfurt/Main
Hoechst AG Frankfurt/Main
Clariant GmbH Frankfurt am Main
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability: (4) not assignable
secondary citation
03-MAY-2002 (30)

Type: LD50
Species: rabbit
Value: = 1280 mg/kg bw

Reliability: (4) not assignable
secondary citation
07-JUN-2002 (26) (27)

Type: LDLo
Species: guinea pig
Strain: no data
Sex: no data
Vehicle: other: mixture of propylene glycol and ethylalcohol
Doses: 783 mg/kg as an 8.7% solution in the vehicle
Value: = 783 mg/kg bw

Year: 1958
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid, purity not specified

Result: Symptoms included ataxia and rapid respiration. Deaths were not delayed.
Reliability: (4) not assignable
Short summary. No further details on methodology available.
07-JUN-2002 (31) (23)

Type: LD50
Value: = 832 mg/kg bw

Reliability: (4) not assignable
secondary citation; no further details given
09-JUN-2002 (31)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

Type: other: approx. LD50
Species: guinea pig
Strain: no data
Sex: no data
Vehicle: other: 90:10 acetone:corn oil
Doses: 5; 10; 20 cc/kg (appr. 500; 1000; 2000 mg/kg bw) as a 10 % solution in vehicle
Value: = 1000 - 2000 mg/kg bw

Method: other
Year: 1954
GLP: no
Test substance: other TS: 3-hydroxy-2-naphthoic acid, purity not stated

Method: 1 animal/dose level. Occlusive treatment (rubber cuff and gum pads). 24 hours exposure. No further detail available.
Result: Slight to moderate edema, slight to moderate redness, necrotic area which in highest dose covered about 1/2 of total area. No further detail available.
Reliability: (2) valid with restrictions
poor documentation; small number of animals
Flag: Critical study for SIDS endpoint
07-JUN-2002 (32)

5.1.4 Acute Toxicity, other Routes

Type: LDLo
Species: rat
Strain: no data
Sex: no data
Vehicle: other: mixture of propylene glycol and ethyl alcohol
Doses: 100 mg/kg as an 8.7% solution in the vehicle
Route of admin.: i.p.
Value: = 100 mg/kg bw

Method: other
Year: 1958
GLP: no
Test substance: other TS: 3-hydroxy-2-naphthoic acid, purity not stated

Result: Symptoms included ataxia and rapid respiration. Deaths were not delayed.
Reliability: (4) not assignable
Short summary. No further details on methodology available.
07-JUN-2002 (31) (23)

Type: other: LDL0
Species: guinea pig
Strain: no data
Sex: no data
Vehicle: other: mixture of propylene glycol and ethyl alcohol
Doses: 200 mg/kg as an 8.7% solution in the vehicle
Route of admin.: i.p.
Value: = 200 mg/kg bw

Method: other
Year: 1958
GLP: no
Test substance: other TS: 3-hydroxy-2-naphthoic acid, purity not stated

Result: Symptoms included ataxia and rapid respiration. Deaths were not delayed.
Reliability: (4) not assignable
Short summary. No further details on methodology available.
09-JUN-2002 (31) (23)

Type: other: approx. LD50
Species: guinea pig
Strain: no data
Sex: male
Vehicle: other: corn oil
Doses: 50-800 mg/kg bw as a 10% suspension in the vehicle
Route of admin.: i.p.
Value: = 100 - 200 ml/kg bw

Method: other
GLP: no
Test substance: other TS: 3-hydroxy-2-naphthoic acid, purity not stated

Method: 5 male animals in total.
Result: Symptoms included weakness, ataxia, unconsciousness and convulsion in highest dose.
Reliability: (2) valid with restrictions

small number of animals; poor documentation
07-JUN-2002 (23)

Type: LDLo
Species: rat
Route of admin.: s.c.
Value: = 376 mg/kg bw

Method: other
GLP: no data
Test substance: no data

Source: Hoechst AG Frankfurt/Main
Hoechst AG Frankfurt/Main
Clariant GmbH Frankfurt am Main
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability: (4) not assignable

secondary citation
03-MAY-2002 (33)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: 500 mg
Exposure: Semiocclusive
Exposure Time: 4 hour(s)
No. of Animals: 3
Vehicle: other: polyethylene glycol
PDII: .3
Result: slightly irritating

Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: 1983
GLP: yes
Test substance: other TS: BONS TTR, technical product, impurity: ca 1% 2-naphthol

Method: The test substance was moistened with polyethylene glycol.
Result: Very slight erythema and oedema (both barely perceptible) were observed 1 hour and 24 hours after removal of the patches. The effects were completely reversible at 48 hours. Mean Draize scores for erythema and edema were 0.3 each.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (34)

Species: guinea pig
Concentration: 12 % active substance
Exposure: no data
Exposure Time: 24 hour(s)
Vehicle: other: mixture of acetone and olive oil

Method: other
Year: 1958
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid; purity not stated

Method: A 12% solution of the test substance in a mixture of acetone and olive oil was held in contact with the depilated skin for 24 hours. Dose and number of animals not stated.
Result: The skin became edematous, necrotic, and there was some subcutaneous hemorrhage in the highest dose. There was evidence of dermal absorption since the animal receiving the highest dose died in twenty-four hours. According to the authors, the test substance caused moderate skin irritation.
Reliability: (4) not assignable
Short summary. No further details available.
Flag: Critical study for SIDS endpoint

09-JUN-2002 (23)

Species: guinea pig
Concentration: 10 % active substance
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 3
Vehicle: other: 10% in 90:10 acetone:corn oil (=about limit of solubility)
Result: irritating

Method: other
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid; purity not specified

Method: 5-20 ml/kg; rubber cuff and gum pads.
Result: Slight to moderate edema, slight to moderate redness, necrotic area which in highest dose covered about 1/2 of total area.
Reliability: (2) valid with restrictions
Poor documentation; occlusive treatment; exposure period exceeds current practices; small number of animals
Flag: Critical study for SIDS endpoint
30-AUG-2004 (32)

Species: rat
Exposure: no data

Method: other: no data
GLP: no data
Test substance: other TS: 3-Hydroxy-2-naphthoic acid; purity not stated

Result: Hyperemia, inflammatory changes, fissures and scabs resulted from the repeated application of 3-hydroxy-2-naphthoic acid to the skin of rats (no further details).
Reliability: (4) not assignable
secondary citation
09-JUN-2002 (27)

Concentration: no data
Exposure: no data

Method: other: no data
Year: 1964
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid, undiluted and diluted; purity not stated

Result: The diluted compound was moderately irritating to the skin, while the undiluted compound was non-irritating.
Reliability: (4) not assignable
No details on species, conditions of contact or vehicle.
06-JUN-2002 (29)

5.2.2 Eye Irritation

Species: rabbit
Dose: 100 other: mg
Exposure Time: 24 hour(s)
Comment: rinsed after (see exposure time)
No. of Animals: 3
Vehicle: other: polyethylene glycol 400
EC classificat.: risk of serious damage to eyes

Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: 1983
GLP: yes
Test substance: other TS: purity ca. 98.5%, impurity: 2-naphthol, ca. 1%

Method: The test substance was moistened with Polyethylene Glycol 400 (0.1 mL); eyes were examined after 1, 24, 48, 72 hours and on day 7 and 14 after application.
Result: 1 hour after application, swelling and conjunctival injection as well as secretion (clear, tinted by the test substance) were observed in all animals.
At 24, 48 and 72 hours, conjunctivitis and diffuse corneal opacities were found. One animal showed iritis at 24 and 48 hours.
7 days after the application, corneal vascularization was observed in all animals.
Mean scores: corneal opacity: 1.1, iris: 0.2, conjunctivitis: 1.9, conjunctival swelling: 1.3.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (35)

Species: rabbit
Concentration: undiluted
Result: slightly irritating

Method: other
Year: 1964
GLP: no
Test substance: other TS: 3-Hydroxy-2-naphthoic acid, undiluted; purity not specified

Result: The undiluted compound produced transient mild irritation of a rabbit eye.
Reliability: (4) not assignable
Short summary. No further details available.
07-JUN-2002 (29)

Species: rabbit

Result: Application of the (presumably) neat substance to the rabbit

conjunctival sac produced gross destructive changes.
Reliability: (4) not assignable
secondary citation
06-JUN-2002 (27)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Concentration 1st: Induction 2 % active substance intracutaneous
2nd: Challenge .25 % active substance occlusive epicutaneous
No. of Animals: 10
Vehicle: other: paraffin (induction); vaseline (challenge)
Result: not sensitizing
Classification: not sensitizing

Method: OECD Guide-line 406 "Skin Sensitization"
Year: 1988
GLP: yes
Test substance: other TS: purity ca. 98.5%, impurity: 2-naphthol, ca. 1%

Method: Strain/Sex: Female Pirbright White guinea pigs.
Number of animals: 10 / group (5 in the control group)
Result: No signs of systemic toxicity were observed during the study.
There was no influence on the body weight.

At challenge, neither the animals of the test group nor the animals of the control group showed any effects.
Reliability: (2) valid with restrictions
limited number of animals. No information on positive controls.
Flag: Critical study for SIDS endpoint
09-JUN-2002 (36)

Type: Patch-Test
Species: human
Vehicle: other: 1% in petrolatum
Result: not sensitizing

Year: 1980
GLP: no
Test substance: other TS: 2-hydroxy-3-naphthoic acid, recrystallized twice from commercial sample

Method: The tests were performed with Finn Chambers on Scanpor. The application was performed on the back for 2 days (48-hr covered contact). Readings were made according to the ICDRG classification 24 hours after the patches were removed.

Patch test concentration: 1% 3-hydroxy-2-naphthoic acid in petrolatum.
Result: Eight patients suffering from pigmented contact dermatitis were patch tested with Sudan I (0.1 % in petrolatum) and its several chemical analogues. None of the patients had a positive reaction towards 3-hydroxy-2-naphthoic acid (tested as 1% in petrolatum). 28 healthy female volunteers, aged 20 and 21, were also tested with these samples as controls. None had a positive reaction.
Reliability: (2) valid with restrictions

small number of subjects
Flag: Critical study for SIDS endpoint
09-JUN-2002 (37)

Type: other: "drop on test"
Species: guinea pig
Concentration 1st: Induction .1 other: M open epicutaneous
2nd: Challenge .1 other: M open epicutaneous
No. of Animals: 5
Vehicle: other: "guinea pig fat extracts"
Result: not sensitizing

Method: other
Year: 1954
GLP: no
Test substance: other TS: purity not stated

Method: controls (5 animals per group): solvent control and positive control (phenylhydrazine, 0.1M in Dioxane Extract of guinea pig fats); no information on application site; "initial scores" and "final scores" were taken at 24 and 48 hours after each of two application. No information is available regarding the time period between induction and challenge treatment.
Remark: controls were functional.
The test concentration is equivalent to 1.88 %.
Reliability: (3) invalid
method does not meet current standards. Poor documentation.
06-JUN-2002 (32)

Type: other: modified guinea pig maximization test
Concentration 1st: Induction 1 % active substance intracutaneous
2nd: Induction 10 % active substance occlusive epicutaneous
3rd: Challenge 1 % active substance open epicutaneous
No. of Animals: 9
Vehicle: other: acetone
Result: sensitizing

Method: other: OECD guideline 406 with modifications
Year: 1985
GLP: no data
Test substance: other TS: 3-hydroxy-2-naphthoic acid from Katayama Chemicals, commercial grade

Remark: Deviation from OECD TG 406: challenge was performed by OPEN epicutaneous application of the test substance solution.
Result: The challenge was performed with 0.1 and 1 % preparations of the test substance in acetone. None out of 9 animals showed skin effects at the reading at 24 hours. At 48 hours, 6 out of 9 animals had positive reactions towards the 1 % preparation, but did not react towards 0.1 %.
Reliability: (2) valid with restrictions
purity of test substance not stated; the deviation from OECD TG 406 is not considered to compromise the reliability of the test result.
Flag: Critical study for SIDS endpoint
09-JUN-2002 (38)

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 10 days
Frequency of treatment: no data
Post exposure period: 2 weeks
Doses: 100 mg/m3
Control Group: no data specified
LOAEL: = 100 mg/m³

Method: other: no data
Year: 1979
GLP: no
Test substance: other TS: purity not stated

Result: Kidney disturbances and increases in blood urea/nitrogen levels and urinary concentrations of urea, protein and chlorides were observed. These changes persisted when the animals were examined 2 weeks after exposure had stopped. Tissue examination revealed kidney changes including necroses.
In studies of "chronic" duration (exposure period not specified, presumably 6 months) the same investigators reported that 0.6 mg/m3 was a "threshold" concentration whereas exposure at 20 mg/m3 caused kidney effects (no further details are given).
Reliability: (4) not assignable
secondary citation.
Flag: Critical study for SIDS endpoint
09-JUN-2002 (27)

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Wistar
Route of administration: gavage
Exposure period: 28 days
Frequency of treatment: 7 d/w
Post exposure period: no
Doses: 0; 12; 60; 300 mg/kg bw
Control Group: yes, concurrent vehicle

Method: other: OECD Guideline 407 (1981)
Year: 1989
GLP: yes
Test substance: other TS: purity ca. 98.5% (impurity: 2-naphthol, ca. 1%)

Remark: Age at study initiation: ca. 6 weeks.
No. of animals per sex per dose: 5.
Vehicle: aqueous carboxymethylcellulose.
Satellite groups: none.
Clinical observations: twice daily.
Functional observations (not specified), and examination of eyes, oral cavity and teeth: at weekly intervals.
Body weights: determined at beginning of the study and then twice per week.
food consumption: determined twice per week.
water consumption: determined once per week.

Haematology/Clinical chemistry/Urinalysis: at study end from all animals.
Organs/tissues examined at necropsy (macroscopic and microscopic): heart, lung, liver, kidneys, spleen, stomach, jejunum, colon, thymus, testes, adrenals, bone marrow.
Statistics: various methods (not specified), significance level p=0.05

Result: The administration of the test substance had no influence on body weights, food consumption and behaviour of the animals. No mortality was observed. There were no neurological impairments, no eye opacities and no pathological findings in the oral cavity or teeth.
300 mg/kg bw: an increased water consumption was observed during the first two study weeks; at the end of the study, a significant decrease in serum phosphate, and an increase in serum bilirubin levels were observed when compared to the controls (the levels were within the normal range of the historical controls). In both sexes, bilirubin was found in the urine (ca. 35 umol/L) and serum. Females showed a slight, but statistically significant increase in liver weights (without histopathological correlate)(no further details available).
At histopathology, one out of five females of the high-dose and one out of five female of the mid-dose group showed adrenal necroses. Examination of the animal from the intermediate dose group revealed diffuse necrosis of the right adrenal cortex. Complete necrosis of the adrenal cortex was detected in the female of the high dose group. Liver fibrosis, and changes in the lobular structure were microscopically seen in one of the females of the low-dose group, but considered as a chance event due to the lack of a dose-response.
In conclusion, decreased serum phosphate levels were observed in both sexes at a dose level of 300 mg/kg bw. The toxicological relevance of this finding is unclear. At 300 mg/kg, increased bilirubin concentrations were found in serum and urine, which may be indicative for a hepatotoxic action of the test compound. Females showed slightly increased liver weights, but without microsocpic correlates. Necroses of the adrenal cortex were found in one female each of the mid- and high-dose group.
NOAEL: 60 mg/kg bw/d (males), 12 mg/kg bw/d (females).

Reliability: (2) valid with restrictions
Limited scope of clinical/organ/tissue examinations; only summary report available

Flag: Critical study for SIDS endpoint

09-JUN-2002 (39) (40)

Type: Sub-acute
Species: rat **Sex:** no data
Strain: no data
Route of administration: gavage
Exposure period: not specified
Frequency of treatment: no data
Post exposure period: no data
Doses: 0.1 LD50 (presumably 245 mg/kg bw d)
Control Group: no data specified

Method: other: no data
Test substance: other TS: purity not stated

Result: Disturbances of kidney function. Increases were noted in the blood nitrogen levels and urinary levels of urea and protein.
Reliability: (4) not assignable
secondary citation. No further details given.
06-JUN-2002 (27)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538; Escherichia coli WP2uvrA
Concentration: 0; 4; 20; 100; 500; 1,000 ug/plate
Cytotoxic Concentration: at concentrations equal or greater 500 ug/plate
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1982
GLP: no
Test substance: other TS: purity not stated

Remark: Metabolic activation: liver S-9 mix from Aroclor induced rats); vehicle: dimethylsulphoxide (DMSO); positive controls: sodium azide, 9-aminoacridine, 2-nitrofluorene, MMNG, aminoanthracene, benzo(a)pyrene; statistical method: not stated.
Result: In a pre-test, cytotoxicity was observed at concentrations of 500 - 2,500 ug/plate (thinning of the bacterial lawn and reduction in the number of colonies). For the mutagenicity testing 1,000 ug/plate was therefore chosen as the highest concentration.
The test substance did not induce increases in the number of colonies in all but one of the tester strains either in the absence or presence of S9 mix. A small increase in the number of colonies was observed with TA1537 in the absence of metabolic activation. This effect could not be reproduced in a second independent experiment.
The authors concluded that the test substance was not mutagenic in the Ames test.
Concurrent positive and negative controls were functional.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
09-JUN-2002 (41) (42)

Type: Cytogenetic assay
System of testing: V 79 hamster lung cells
Concentration: without S9: 0; 75; 250 ug/mL (18h) and 750 ug/mL (6,18, 28h);
with S9: 0; 10; 75 ug/mL (18h) and 150 ug/mL (6, 18, 28h)
Cytotoxic Concentration: no cytotoxicity observed
Metabolic activation: with and without
Result: positive

Method: OECD Guide-line 473
Year: 1989
GLP: yes
Test substance: other TS: purity 98.5% (impurity: 2-naphthol, ca. 1%)

Method: metabolic activation: liver S-9 mix from Aroclor induced rats; statistical method: Fisher`s exact test. Vehicle: methanol; positive controls: EMS (2000 ug/mL), cyclophosphamide (5ug/mL). 100 metaphases per group were examined.
Remark: only summary report available.
Result: The test substance induced a significant increase in the number of chromosome aberrations 18 hours after treatment with 750 ug/mL in the absence of metabolic activation. The types of chromosome aberrations included breaks, fragments, deletions, and exchanges. This increase was substantially greater than the increase induced by the positive control material. A slight increase of aberrations (including gaps) was observed at 750 ug/mL 6 hours after treatment (without S9). The test substance was NOT clastogenic in the presence of metabolic activation.
A significant cytotoxic effect was not observed (in a pre-test concentrations of 1000 ug/mL (without metabolic activation) and of 200 ug/mL in the presence of S9 mix were highly cytotoxic).
Concurrent positive and negative controls were functional.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (43) (42)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538; Escherichia coli WP2uvrA
Concentration: 0; 1; 5; 10; 50; 100; 500; 1,000; 5,000 ug/plate
Cytotoxic Concentration: 5,000 ug/plate
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1985
GLP: no data
Test substance: other TS: purity 99.9%

Method: metabolic activation: liver S-9 mix from PCB induced SD rats. Vehicle: dimethylsulphoxide (DMSO); positive controls: AF-2, ENNG, 9-aminoacridine, 4NQO, B(a)P, 2AA, 2-nitrofluorene.
Remark: The positive controls were functional.
Result: The test substance was not mutagenic in the Ames test, either in the presence or in the absence of metabolic activation.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (44)

Type: Ames test
System of testing: Salmonella typhimurium strains (not specified), Escherichia coli WP2uvrA
Concentration: up to 5 mg/plate
Cytotoxic Concentration: no data
Metabolic activation: with and without
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: other TS: purity not stated

Result: Overall 3-hydroxy-2-naphthoic acid was judged by the study authors to be non-mutagenic in the Ames test either with or without S9. Only in the absence of S9, a very weak mutagenic activity was seen in two of the tested strains (TA 1537 and TA 1538). No further details available.
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
06-JUN-2002 (45)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: Chinese hamster **Sex:** male/female
Strain: other: Han:Chin
Route of admin.: gavage
Exposure period: single application
Doses: 0; 2000 mg/kg bw
Result: negative

Method: OECD Guide-line 475 "Genetic Toxicology: In vivo Mammalian Bone Marrow Cytogenetic Test - Chromosomal Analysis"
Year: 1993
GLP: yes
Test substance: other TS: purity 97,9%

Method: The test substance was suspended in starch mucilage and dosed once orally at 2000 mg/kg bw to male and female Chinese hamsters, based upon the results of a previous dose range finding study.
5 males and 5 females per group were killed 12, 24 or 48 hours after treatment.
Endoxan was used as a positive control substance and was administered orally at a dose of 50 mg/kg bw. The animals of the positive control group were killed 24 hours after treatment.
Animals treated with the vehicle alone were used as negative controls. 5 males and 5 females each were sacrificed at 12, 24 or 48 hours after treatment.
Two hours before sacrifice, each of the animals received an intraperitoneal injection of 3.3 mg demecolcin (Colcemid) / kg bw. The bone marrow was obtained from the femora of the animals. 2-4 slides were prepared from each animal and 50 metaphases per animal were evaluated for numerical and structural chromosome aberrations.
Statistics: not performed, as all aberration rates were within the range of the negative control values.
Result: The test substance did not induce a significant increase in the number of chromosomal aberrations. A marked increase in the number of chromosomal aberrations was found in the groups treated with the positive control substance.

The numbers of metaphases with aberrations (excluding gaps) was as follows:
at 12 hours: neg control - 0%, test substance - 0%
at 24 hours: neg control - 0.2%, test substance - 0%, positive control - 13.0%
at 48 hours: neg control - 0%, test substance: 0.2%.
The numbers of metaphases with aberrations (including gaps) was as follows):

at 12 hours: neg control - 0.4%, test substance - 1.6%
at 24 hours: neg control - 0.8%, test substance - 0.8%, positive control - 14.0%
at 48 hours: neg control - 0.4%, test substance: 1.8%.

No clinical signs of toxicity were observed. There was no sign of cytotoxicity in the bone marrow cells (no reduction of the mitotic index). At necropsy, no pathological changes were found.

Reliability: (2) valid with restrictions
In deviation from OECD TG 475, only 50 metaphases were scored per animal.

Flag: Critical study for SIDS endpoint

09-JUN-2002 (46) (42)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

Type: One generation study
Species: rat
Strain: Sprague-Dawley
Route of administration: gavage
Exposure Period: males: for 10 weeks prior to mating, during the mating period and until the day before necropsy (98 days); females: for 2 weeks prior to mating, during mating and gestation and until day 20 of lactation
Frequency of treatment: daily
Premating Exposure Period
male: 10 weeks
female: 2 weeks
Doses: 0; 12.5; 50; 200 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL F1 Offspring: = 50 mg/kg bw

Method: OECD Guide-line 415 "One-generation Reproduction Toxicity Study"
Year: 2000
GLP: yes
Test substance: other TS: purity 99.2%, impurity: 2-naphthol, 0.1%

Method: Vehicle: 0.5% sodium carboxymethylcellulose solution.
number of animals: 25 per sex per dose group.
Age at initiation: 5 weeks (males), 10 weeks (females).
Mating period: max 3 weeks (1:1, until pregnancy or until three weeks had elapsed).
Males were sacrificed 1 week after the mating period. Before necropsy, blood samples were taken. Principal organs, pituitary gland, stomach, adrenal glands, testes, epididymides, coagulating glands, seminal vesicles and prostate were isolated and examined. The organs from the control and the high-dose group and all organs with macroscopic abnormalities were processed for histopathological examinations.
Pregnant females were allowed to deliver spontaneously and were sacrificed on day 21 of lactation together with their offspring. Test substance was applied until the day before sacrifice. At necropsy, all females were examined for abnormalities of the principal organs, the uteri were

isolated and the number of implantations counted. In addition, pituitary gland, stomach, adrenal glands, ovaries, cervix and vagina were examined. All organs with macroscopic abnormalities were processed for histopathological examinations.
The parent animals were observed for general condition and for changes in body weight and food consumption as well as reproductive ability including parturition and lactation. Each litter was examined for number of pups born (live and dead newborns); live newborns were examined for presence of gross anomalies. All dead pups were examined by necropsy. The offspring were also observed for development up to weaning. On day 4 after birth, the size of each litter was adjusted to 8 pups (four males and four females, in principle). Adjustment was not performed for litters of less than eight pups. Eliminated pups were examined for abnormalities by gross necropsy and fixed in formalin. Live pups were individually weighed on days 0,4,7,14 and 21 after birth, and mean pup weight in each litter was calculated by sex. On day 21 after birth, all live pups were sacrificed and examined for abnormalities by gross necropsy. Organs with abnormalities were fixed in formalin solution.
Statistical analysis: frequency/length of estrous cycle, copulation and fertility indices and frequency of offspring with morphological abnormalities were analyzed by Fisher`s exact probability test. Differences in histopathological findings, the graded data and total numbers of postitives were analyzed by Mann-Whitney`s U-test and one-tailed Fisher`s exact probability test, respectively. Individual data or mean values of each litter were treated as a single sample, and homogeneity of variance of these samples among groups was analyzed using Bartlett`t test. When homogeneity of variance was confirmed, one-way analysis of variance was applied to detect significance between groups. If a significant difference was detected, the Dunnett`s test was applied for multiple comparisons. When variance was not homogenous or zero, the Kruskal-Wallis analysis of ranks was applied, and, if significance was detected, the Dunnett`s test applied for multiple comparisons. Significance levels: p=0.01 and 0.05.

Result: Males:

1 animal of the control group died from malocclusion.
Each one animal in the low- and mid-dose group was killed in a moribund state or died from myelogenous leukemia which was considered as not related to treatment by the study authors.

200 mg/kg bw: transient salivation and nasal discharge were observed after dosing. Body weight gain was significantly decreased (- 35-40% vs control) in the terminal study period (days 85-99).

12.5 and 50 mg/kg bw had no effects on general condition, body weight gain and food consumption.

No abnormalities were found at the hematological examination at necropsy with the exception of a slight, but statistically significant increase in the red blood cell count in the mid- and high dose group (+6%, +8% vs control). At necropsy, thickening of the mucosa of the forestomach was observed in 6 animals of the high-dose group.

Histopathological examination revealed hyperplasia of the forestomach squamous epithelium in the animals of the mid- and high-dose groups. Three animals of the high dose group showed enlarged livers without histopathological changes. No histopathological changes were found in bone marrow, spleen, adrenals, pituitary glands, testes, epididymides, coagulating glands, seminal vesicles and prostates. 12.5 mg/kg bw caused neither macroscopic nor microscopic changes.

Females:

Neither deaths nor moribund condition were observed in any group.
200 mg/kg bw: transient salivation was observed after dosing. Body weight gain was significantly decreased in the early study phase (days 1-8 of treatment: - 60% vs control), as well as in the terminal period of pregnancy (- 12%) to day 4 of lactation (-70%). 200 mg/kg bw had no influence on food consumption.

12.5 and 50 mg/kg bw had no effects on general condition, body weight gain and food consumption.

At necropsy, one female of the high-dose group showed thickening of the forestomach mucosa, and had squamous epithelial hyperplasia of the forestomach. No changes were found in adrenals, pituitary glands, ovaries, uterus, cervix and vagina. 50 and 12.5 mg/kg bw did not cause any macroscopic or microscopic changes. There was no significant difference in the number of implants between treated and control groups.

Reproductive Performance:

All females showed normal estrous cycle, and all animals performed fertile copulation. No adverse effect of the test substance was observed on pairing days until conception and number of vaginal estrous during the mating period. Furthermore, no abnormality was found in delivery and nursing conditions, and no adverse effects of the test substance on gestation index and gestation length were found. According to the authors of the study, 200 mg/kg bw could however suppress lactation, since the body weight of the offspring in this group was decreased.

Offspring:

Administration of the test substance did not affect viability and general condition, including behaviour of the offpring. There was no effect on the number of stillbirth, number of live pups, delivery index, birth index, sex ratio, viability index and weaning index.

Decreased body weights were found in the pups of both sexes in the high-dose group from birth (-15%), until day 21 (-9%).
No effects on body weight were seen in the low- and mid-dose groups.
There was an increase in the incidence of offspring with external malformations, such as kinked tail (n=1), brachyury (5), brachyury with kink (1) or microphthalmus (1, dead

offspring) in the high-dose group (offspring from 2 out of 25 dams; no pup in the control showed morphological changes). In addition, there were two dead offspring of two dams with visceral malformations in this group, such as undescended testes, hypoplasia of the spleen or diaphragmatic hernia. Although all these malformatins were found only in offspring of few limited litters, teratogenicity of the compound could not be ruled out from the present results according to the authors of the study.

NOEL for reproductive toxicity, males: 200 mg/kg bw.
NOEL for reproductive toxicity, females and offspring: 50 mg/kg bw. Growth retardation and teratogenicity was observed at 200 mg/kg bw.
NOEL for systemic toxicity, males: 12.5 mg/kg bw (forestomach lesions at 50 mg/kg bw)
NOEL for systemic toxicity, females: 50 mg/kg bw (reduced body weight gain, forestomach lesions at 200 mg/kg bw).

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (47)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Doses: 0; 12.5; 50; 200 mg/kg bw
NOAEL Maternal Toxity: = 50 mg/kg bw
NOAEL Teratogenicity: = 50 mg/kg bw
Result: There was an increase in the incidence of offspring with external malformations such as kinked tail, brachyury, brachyury with kink or microphthalmus in the high-dose group. For detailed study results, cf. section on "Toxicity to Fertility"

Method: other: OECD Guideline 415 (1983)
Year: 2000
GLP: yes
Test substance: other TS: purity 99.2%, impurity: 2-naphthol, 0.1%

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
09-JUN-2002 (47)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Type of experience: Human

Remark: No relevant occupational health effects have been reported for workplaces at exposure levels below 1 mg/m3. At higher exposures, skin and mucosal irritation were observed, beginning with itching of the skin.

Source: Hoechst AG Frankfurt/Main
Hoechst AG Frankfurt/Main
Clariant GmbH Frankfurt am Main
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability: (4) not assignable
short summary, no methodological details available
Flag: Critical study for SIDS endpoint
06-JUN-2002 (48)

Type of experience: Human

Remark: summarized Dec 10, 1964
Result: Available human experience in the manufacture and handling of 3-hydroxy-2-naphthoic acid did not present evidence of injury secondary to this exposure.
Reliability: (4) not assignable
short summary. No methodological details available.
Flag: Critical study for SIDS endpoint
06-JUN-2002 (49)

Type of experience: Human

Result: Pustulent skin disease was reported in a group of 42 workers
exposed to 3-hydroxy-2-naphthoic acid. The investigators suggested that skin irritation could have played a role in this finding (no further details were given).
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
06-JUN-2002 (27)

Type of experience: Human

Result: It was reported that over a 4-year period the freqency of illness was higher in a group of 42 workers exposed to 3-hydroxy-2-naphthoic acid than in a control group. Catarrhal infection of the upper respiratory tract was apparently a notable effect. The investigators suggested that local irritation by 3-hydroxy-2-naphthoic acid could have increased the workers susceptibility. Brief statement, no further details were given.
Reliability: (4) not assignable

Flag: Critical study for SIDS endpoint
06-JUN-2002 (27)

5.11 Additional Remarks

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(3) BIBRA working group. 2-Hydroxy-3-Naphthoic Acid. Toxicity profile. BIBRA International, 1999

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(25) Hoechst AG (1984): Unpublished study. BONS TRTR Prüfung der akuten oralen Toxizität an der männlichen und weiblichen Wistar-Ratte (in German) (Ber. 83.0665), 5 Jan 1984

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