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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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1,8-Naphthalic anhydride No. 256

CAS No. 81-84-5

BG Chemie
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1,8-Naphthalic anhydride

1 Summary and assessment

1,8-Naphthalic anhydride exhibits low toxicity following acute oral administration, dermal application and inhalation (LD_{50} rat oral 9600 and 12340 mg/kg body weight, depending on the source of information; LD_{50} rabbit dermal > 2025 mg/kg body weight; exposure of rats to dust for 4 hours at a concentration level of 420 mg/m³ was tolerated without findings). Following intraperitoneal administration the LD_{50} values for the rat and the mouse range from 200 to 480 mg/kg body weight. Lethargy, weakness, piloerection, decreased respiratory rate, increased salivation, ptosis, tremors, diarrhoea, increased diuresis and blood in the urines, amongst others, have been described as signs of toxicity. Autopsy findings reported after oral administration of lethal doses include slight haemorrhage of the lungs and discolouration of the liver, the spleen and the kidneys. The post-mortems performed on the surviving animals at the end of the 14-day observation period showed no abnormal findings.

Daily oral administration to rats of 1,8-naphthalic anhydride given at doses of 2000 mg/kg body weight per day for 30 days has been reported to lead to reductions in the numbers of red blood cells and reticulocytes as well as in the haemoglobin content of the blood, to lead to hypergammaglobulinaemia, increases in relative liver weight, vitamin C content of the liver and elevated ceruloplasmin levels in blood serum, to proteinuria, reduction in creatinine concentration in the urine and to an increase in relative kidney weights. In addition, 20 dermal exposures to a 30-percent aqueous solution of 1,8-naphthalic anhydride, each lasting 4 hours, (no indication of the species used in the test) have been reported not to produce any changes in the skin, but to cause increases in haemoglobin and chloride levels as well as increased leukocyte counts, a reduction in copper oxidase activity and changes in the parameters which characterise the central nervous system. However, on account of the inadequacies in documentation and conduct of the studies in question (e. g. only one dose per test, lack of information on any controls which may have been carried out and the species and/or strains as well as the numbers of animals used, the size and scope of the studies, the time points of observation and the purity of the test substance),

these studies are not suitable for the evaluation of the systemic toxicity of 1,8-naphthalic anhydride after repeated administration.

In the patch test, which was conducted according to The Code of Federal Regulations, Title 16, Section 1500.41, 24-hour application of 1,8-naphthalic anhydride under occlusive cover did not exhibit any irritant effect on either the intact or the scarified skin of the rabbit. In a mucous membrane irritation study conducted in rabbits in accordance with OECD guideline No. 405, application of 1,8-naphthalic anhydride produced low-grade reversible irritation of the eye. Applying the criteria laid down in EC guideline No. 67/548/EEC, the substance was not classified as a mucous membrane irritant in the light of the findings of the study.

In the guinea pig, 1,8-naphthalic anhydride exerts a sensitising effect in the maximisation test as described by Magnusson and Kligman.

Without specifying any details, it has been reported that in a 90-day feeding study in the rat and the dog, administration of 500 mg of 1,8-naphthalic anhydride/kg feed did not lead to appreciable findings.

In the Salmonella/microsome test conducted in the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and the rec assay in *Escherichia coli* WP2 and WP100, 1,8-naphthalic anhydride did not exhibit any mutagenic effects. The urine and faeces of rats did not contain any detectable amounts of mutagenic metabolites either, as assessed in the *Salmonella typhimurium* strain TA 1538 following a single oral administration of 4800 mg of 1,8-naphthalic anhydride/kg body weight. In vivo, the micronucleus test in the Chinese hamster did not show any evidence of mutagenic potential following a single intraperitoneal administration of up to 3200 mg of 1,8-naphthalic anhydride/kg body weight.

According to communications from two companies' occupational medicine and health care departments, no instances of illness or disease, and in particular no cases of respiratory tract or skin sensitisation, were observed to be causally related to 1,8-naphthalic anhydride exposure in the context of production and use of the substance.

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") or the Deutsche Forschungsgemeinschaft has designated

1,8-naphthalic anhydride with “Sh” for skin-sensitising chemicals in the List of MAK and BAT Values.

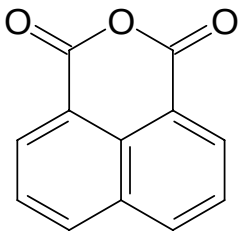
2 Name of substance

2.1	Usual name	1,8-Naphthalic anhydride
2.2	IUPAC name	1H,3H-Naphtho[1,8-c,d]pyran-1,3-dione
2.3	CAS No.	81-84-5
2.4	EINECS No.	201-380-2

3 Synonyms, common and trade names

1,8-Naphthalenedicarboxylic acid anhydride
Naphthalene-1,8-dicarboxylic anhydride
1,8-Naphthalenedicarboxylic anhydride
Naphthalic acid anhydride
1,8-Naphthalic acid anhydride
Naphthalic anhydride
1,8-Naphthalindicarbonsäureanhydrid
Naphthalin-1,8-dicarbonsäureanhydrid
Naphthalsäureanhydrid
1,8-Naphthoic anhydride
Naphtho[1,8,8a-c,d]pyran-1,3-dion
Naphtho[1,8-c,d]pyran-1,3-dione
1H,3H-Naphtho[1,8,8a-c,d]pyran-1,3-dione
NSA
Protect

4 Structural and molecular formulae

4.1	Structural formula		
4.2	Molecular formula	$C_{12}H_6O_3$	

5 Physical and chemical properties

5.1	Molecular mass, g/mol	198.18	
5.2	Melting point, °C	269–274	(Weyl, 1991)
		270–273	(Ciba-Geigy, 1989)
		270–274	(Anonymous, 1991)
		273–274	(Sax, 1995)
		274	(Freitag, 1975; Weast, 1988)
		275	(Eastman Kodak, 1970)
		276	(Röhrscheid, 1986)
5.3	Boiling point, °C	215 (sublimes; at 4,4 hPa)	(Röhrscheid, 1986)
		301 (at 53 hPa)	(Freitag, 1975)
		422 (at 1013 hPa)	(Röhrscheid, 1986)
5.4	Vapour pressure, hPa	No information available	
5.5	Density, g/cm³	0.3–0.31 (bulk density)	(Weyl, 1991)
5.6	Solubility in water	< 0.1 g/l (at 20 °C)	(Weyl, 1991)
		0.1 g/l (at 23 °C)	(Rütgerswerke, 1985)
5.7	Solubility in organic solvents	Low solubility in acetic acid	(Sax, 1995)
		Dissolves well in alcohol and ether	(Röhrscheid, 1986; Sax, 1995)
		Soluble in dimethylformamide (13.9 g/l)	(Worthing and Walker, 1987)
5.8	Solubility in fat	Partition coefficient n-octanol/water, log P_{ow} 0.1536 (measured)	(Rütgerswerke, 1991)
5.9	pH value	6.6 (at 0.1 g/l)	(Rütgerswerke, 1985)

5.10	Conversion factor	1 ml/m³ (ppm) ≙ 8.11 mg/m³ 1 mg/m³ ≙ 0.12 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Intermediate used in the manufacture of imides and imide derivatives, in particular imidazole dyestuffs and optical brighteners (Röhrscheid, 1986) as well as seed dressing agents in agriculture (Worthing and Walker, 1987).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

The results from acute toxicity studies of 1,8-naphthalic anhydride following oral administration, dermal application, inhalation and intraperitoneal administration are summarised in Table 1.

Beginning of Table 1

Table 1. Acute toxicity studies of 1,8-naphthalic anhydride

Species, strain, sex*	Route of administration	Dose (mg/kg body weight, or mg/m³)	Purity	Effects	Observation period	Reference
Rat	oral	12340	n. d.	LD_{50}	n. d.	Anonymous, 1991
Rat, CFY, male, female	oral	9600 (administered as a 40-percent suspension (w/v) in aqueous methylcellulose (1%))	n. d.	LD_{50}, death occurred after 23 to 94 hours; lethargy, piloerection, decreased respiratory rate, diarrhoea, increased diuresis, salivation, ptosis, tremors; post-mortems on the deceased animals: slight haemorrhages in the lungs, discolouration of the liver, spleen and kidneys (no further details); surviving animals: no clinical signs at the end of the observation period, no autopsy findings	14 days	HRC, 1977a
Rat	oral	> 3200 (10% administered in 0.5% guar gum)	n. d.	LD_{50}, death occurred after 1 to 4 days, depending on the dose given (200 to 3200 mg/kg body weight were administered): no findings, and moderate weakness, blood in urines, diarrhoea, respectively	14 days	Eastman Kodak, 1970
Mouse	oral	1600–3200 (10% administered in 0.5% guar gum)	n. d.	LD_{50}, death occurred after 2 days, depending on the dose given (200 to 3200 mg/kg body weight were administered): slight to distinct weakness, tremor up to 24 hours after administration	14 days	Eastman Kodak, 1970
Not specified (but presumably rat and/or mouse)	oral	6000–8000	n. d.	not lethal	n. d.	Reznichenko et al., 1989
Rabbit	dermal	> 2025	n. d.	LD_{50}	n. d.	Worthing and Walker, 1987

Table 1. Acute toxicity studies of 1,8-naphthalic anhydride						
Species, strain, sex*	Route of administration	Dose (mg/kg body weight, or mg/m³)	Purity	Effects	Observation period	Reference
Guinea pig	dermal	> 1000	n. d.	LD_{50}, none of the 3 exposed animals died, depressed body weight gain, irritation of the skin, which was reversible within 2 weeks (see Chapter 7.3)	n. d.	Eastman Kodak, 1970
Rat	inhalation (4 hours)	820 mg/m³ (dust)	n. d.	No appreciable findings	n. d.	Worthing and Walker, 1987
Rat, female	intraperitoneal	480	n. d.	LD_{50}, death occurred within 8 days; breathing difficulties, increased irritability, narrowing of the palpebral fissure, convulsions	n. d.	Reznichenko et al., 1989
Rat	intraperitoneal	200–400 (10% administered in 0.5% guar gum)	n. d.	LD_{50}, death occurred after 4 hours to 2 days, depending on the dose given (200 to 3200 mg/kg body weight were administered): slight to distinct weakness, slight spasms, bristled fur	14 days	Eastman Kodak, 1970
Rat, male	intraperitoneal	230	n. d.	LD_{50}, death occurred within 8 days; breathing difficulties, increased irritability, narrowing of the palpebral fissure, convulsions	n. d.	Reznichenko et al., 1989
Mouse, male	intraperitoneal	250	n. d.	LD_{50}, death occurred within 8 days, breathing difficulties, increased irritability, narrowing of the palpebral fissure, convulsions	n. d.	Reznichenko et al., 1989
Mouse	intraperitoneal	200–400 (10% administered in 0.5% guar gum)	n. d.	LD_{50}, death occurred after 4 hours to 8 days, depending on the dose given (200 to 3200 mg/kg body weight were administered): slight to very distinct weakness, dark eyes, spasms	14 days	Eastman Kodak, 1970
* if specified n. d. no data						

End of Table 1

In the rat, 1,8-naphthalic anhydride exhibited low acute toxicity following oral administration, with LD_{50} values ranging from > 3200 to 12340 mg/kg body weight. For the mouse, an exploratory study involving oral administration found an LD_{50} in the range from 1600 to 3200 mg/kg body weight (see Table 1). In acute dermal toxicity studies in the rabbit and the guinea pig as well as in acute inhalation toxicity studies in the rat, 1,8-naphthalic anhydride also exhibited low toxicity (LD_{50} rabbit dermal > 2025 mg/kg body weight; LD_{50} guinea pig dermal > 1000 mg/kg body weight; exposure to dust at a level of 420 mg/m³ for 4 hours was tolerated without appreciable findings in the rat; Eastman Kodak, 1970; Worthing and Walker, 1987). Following intraperitoneal administration, the LD_{50} values for the rat and the mouse were in the range from 200 to 480 mg/kg body weight (Eastman Kodak, 1970; Reznichenko et al., 1989). Lethargy, weakness, piloerection, decreased respiratory rate, increased salivation, ptosis, tremors, diarrhoea, increased diuresis, blood in the urines and other signs of toxicity have been described (see Table 1). The post-mortems conducted after oral administration of lethal doses revealed slight haemorrhage of the lungs and discolouration of the liver, the spleen and the kidneys. Post-mortems on the surviving animals killed at the end of the 14-day observation period yielded no appreciable findings (HRC, 1977a).

Daily oral administration in the rat of 1,8-naphthalic anhydride at a dosage of 2000 mg/kg body weight/day for 30 days is reported to have led to a reduction in the numbers of red blood cells and reticulocytes as well as in the haemoglobin content of the blood. Following 5-day and 15-day administrations, hypergammaglobulinaemia, increases in relative liver weights, vitamin C content of the liver and ceruloplasmin levels in blood serum have been described. Further treatment-related changes reported include proteinuria, reduction in creatinine concentration in the urine and increased relative kidney weights. In addition, the authors reported that 20 dermal exposures to a 30-percent aqueous solution of 1,8-naphthalic anhydride (no indication of the species used in the test), each lasting 4 hours, did not cause changes in the skin, but did lead to an increase in haemoglobin and chloride levels as well as in the numbers of leukocytes, a reduction in copper oxidase activity and changes in the parameters which characterise the central nervous system (no further details; Reznichenko et al., 1989). On account of the inadequacies in documentation and conduct of the studies in question (e. g. only one dose per test, lack of information on any controls

which may have been carried out and the species and/or strains as well as the numbers of animals used, the size and scope of the studies, the time points of observation and the purity of the test substance), these investigations are not suitable for the evaluation of the systemic toxicity of 1,8-naphthalic anhydride after repeated administration.

7.3 Skin and mucous membrane effects

The irritant effect of 1,8-naphthalic anhydride (purity not specified) on the skin was studied in the abraded dorsal skin of rabbits using the patch test in accordance with The Code of Federal Regulations, Title 16, Section 1500.41. Each of 6 rabbits were treated with 500 mg of the test substance (in 0.5 ml of distilled water) for 24 hours by means of application under occlusive cover to the intact and the scarified skin (application area approx. 2.5 cm x 2.5 cm). The findings obtained immediately upon removal of the dressing and in the observation period of 48 hours did not reveal any signs of irritation, and 1,8-naphthalic anhydride was classified as not irritating to the skin of the rabbit (HRC, 1977b).

In 3 guinea pigs receiving a dermal application of 250 to 1000 mg 1,8-naphthalic anhydride/kg body weight, moistened with water, for 24 hours in the framework of an acute dermal toxicity study, moderate to severe oedema, slight to moderate erythema and blister formation were observed at the end of exposure (see also Chapter 7.2, Table 1). One week after application, the skin showed discolouration and desquamation and was without appreciable findings after 2 weeks. The irritant effect of 1,8-naphthalic anhydride on the skin was evaluated as slight by the authors on the basis of these findings (Eastman Kodak, 1970).

In a mucous membrane irritation study (conducted in accordance with OECD guideline No. 405), 100 mg of 1,8-naphthalic anhydride (purity not specified) were applied to the left eye of each of 3 female New Zealand rabbits. The untreated right eyes served as controls. The effects were assessed 1, 24, 48 and 72 hours as well as 4 and 7 days after application. Treatment-related effects observed in all 3 animals were reversible slight conjunctivitis and in one animal additional slight iritis. In 2 animals no appreciable findings were seen 48 hours after application, and in the third animal there were no appreciable findings 7 days after application. The

highest primary irritation index found 24 hours after application was 8.3 from a maximum irritation index of 110. 1,8-Naphthalic anhydride was classified by the authors as slightly irritating to mucous membranes according to the scoring system established by Kay and Calandra, and as a non-irritant to mucous membranes according to EEC directive No. 67/548/EEC (Hazleton, 1986).

In a further study of mucous membrane irritancy conducted in only 2 rabbits, 1,8-naphthalic anhydride was evaluated as slightly irritant to the rabbit eye. Following application of the crystalline dry substance (purity not specified), slight or moderate erythema of the conjunctivae and nictitating membranes were reported. This effect was found to be reversible after 24 hours in one animal, which received an eye rinse after application of the substance, and after 48 hours in the second animal, which was not given an eye rinse (Eastman Kodak, 1970).

7.4 Sensitisation

The skin sensitisation potential of 1,8-naphthalic anhydride (purity of the test substance 99.06%) was assessed in 20 male Dunkin-Hartley guinea pigs using the Magnusson and Kligman maximisation test in accordance with EEC directive No. 92/69/EEC. The control group consisted of 10 male animals and was treated with the formulating agent, Alembicol D, a product of coconut oil. Intradermal induction using an 0.1-percent formulation accompanied by simultaneous intradermal administration of Freund's complete adjuvant was followed after one week by a 48-hour occlusive dermal induction using a 50-percent formulation (minimum irritancy formulation). Dermal challenge, which followed 14 days after the second induction treatment, was accomplished by application under occlusive cover of a 5-percent formulation to an anterior site on the flank of each guinea pig and similar treatment was carried out by applying a 10-percent formulation (maximum non-irritant concentration) to a posterior site on the animal's flank for 24 hours. This challenge led to a clear positive skin reaction in 16 of the 20 animals and produced a questionable positive skin reaction in 1 of the 20 animals. 1,8-Naphthalic anhydride thus exhibited a skin sensitising potential in this test (Huntingdon, 1996).

7.5 Subchronic and chronic toxicity

In 90-day feeding studies in the rat and the dog, administration of 500 mg 1,8-naphthalic anhydride/kg feed produced no appreciable findings (no further details; Worthing and Walker, 1987).

7.6 Genotoxicity

7.6.1 In vitro

In the Salmonella/microsome test using *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538, there were no indications of a mutagenic potential of 1,8-naphthalic anhydride. The test substance with a purity of 91.2% was used in concentrations ranging from 5 to 250 µg/ml (no further details; Rütgerswerke, 1985).

In a further Salmonella/microsome test using *Salmonella typhimurium* strains TA 98 and TA 100, 1,8-naphthalic anhydride showed no mutagenic effect either with or without S9-mix (no further details; Nishi et al., 1986).

In the rat, no mutagenic metabolites were detected with the *Salmonella typhimurium* strain TA 1538 in the urine and faeces following a single oral administration of 4800 mg 1,8-naphthalic anhydride/kg body weight (no further details; Rütgerswerke, 1985).

In the rec assay in *Escherichia coli* WP2 ($uvrA^+$, $recA^+$) and WP100 ($uvrA^-$, $recA^-$) 1,8-naphthalic anhydride exhibited no damaging effect on the DNA (no further details; Nishi et al., 1986).

7.6.2 In vivo

The micronucleus test conducted in bone marrow cells of the Chinese hamster yielded no results indicating mutagenicity. The Chinese hamsters received 1,8-naphthalic anhydride by intraperitoneal administration at single doses of 320 and 3200 mg/kg body weight. The proportion of bone marrow cells containing micronuclei did not exceed the normal average value of 1% (no further details; Rütgerswerke, 1985).

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

No information available.

8 Experience in humans

In a plant for the production of 1,8-naphthalic anhydride a total of 61 workers were employed in the period from 1963 to 1993. The workers were under the company physician's medical supervision. They were not observed to develop any diseases with a causal relation to 1,8-naphthalic anhydride exposure (Rütgerswerke, 1994).

Reports from another company's occupational medicine and healthcare protection department stated that no cases of respiratory tract or skin sensitisation had been observed in connection with the handling of 1,8-naphthalic anhydride (BASF, 1993).

9 Classifications and threshold limit values

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kom-

mission") of the Deutsche Forschungsgemeinschaft has designated 1,8-naphthalic anhydride with "Sh" for skin-sensitising chemicals in the List of MAK and BAT Values (DFG, 1999).

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