Butanone oxime

Supplement 1997

MAK value/classification	**see Section III, Category 2 of the *List of MAK and BAT Values***
Date of evaluation	**1997**
CAS number	96-29-7

Since publication of the documentation from 1979 documentation "Butanonoxim" 1979 (German), further studies have yielded results which make it necessary to re-evaluate the substance.

1 Toxic Effects and Mode of Action

Butanone oxime is taken up orally, dermally and by inhalation. The substance has strong local irritative effects on the mucous membranes. After long-term exposure of rats and mice, damage to the olfactory epithelium was observed even at the lowest concentration tested of 15 ml/m³.

Methaemoglobin was produced after short-term exposure to concentrations of 400 ml/m³ and above; concentrations of around 700 ml/m³ and above led to sedative and narcotic effects with hypoactivity after a phase of agitation. After repeated exposure for up to a year, methaemoglobin was formed even at concentrations of 100 ml/m³, while adaptation was observed after long-term exposure. Enlargement and pigmentation of the spleen, and extramedullary haematopoiesis in the liver are connected with the erythrocyte-damaging effects of butanone oxime.

After long-term inhalation, the most important effects are the hepatotoxic effects in addition to the damage to the olfactory epithelium. In male rats and mice, toxic effects on the liver were observed after concentrations of 15 ml/m³ as well as the local effects. After concentrations of 75 ml/m³ and above, the incidence of liver adenomas in male rats was increased, and butanone oxime concentrations of 375 ml/m³ led to a significant increase in the incidence of liver carcinomas in the male animals. The occurrence of DNA and RNA modifications in the liver of rats exposed to butanone oxime indicates a liver-specific activation of butanone oxime to produce metabolites with genotoxic potential.

In *in vitro* genotoxicity studies, except for one positive mouse lymphoma test without metabolic activation, mostly negative results were obtained (*Salmonella* mutagenicity test, and tests for sister chromatid exchange (SCE), unscheduled

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DNA synthesis (UDS) and chromosomal aberrations), which was probably because butanone oxime is not metabolically activated in these test systems.

Skin sensitizing effects were demonstrated in animal studies. Cases of allergic contact dermatitis in humans, are, however, to date unknown.

In studies with rats and rabbits, butanone oxime caused embryotoxic, but not teratogenic effects after high, maternally strongly toxic doses. In the rat, butanone oxime was not found to have adverse effects on fertility.

2 Mechanism of Action

In animal studies, exposure to butanone oxime leads to the formation of methaemoglobin; this is probably caused by nitrite. After hydrolysis of butanone oxime, butanone and hydroxylamine are formed; the latter can be oxidized to nitrite, which is known to have a methaemoglobin-producing effect (Kiese 1974). Also the changes in the spleen and extramedullary haematopoiesis in the liver are attributed to the erythrocyte-damaging effects.

Butanone oxime causes in addition damage to the olfactory epithelium. Degeneration of the olfactory epithelium is probably the result of the irritative effects of butanone oxime on the mucous membranes.

The mechanisms that lead to liver damage have not been clarified experimentally. The hepatocarcinogenicity of butanone oxime observed in two studies is probably a general property of ketoximes, as also acetone oxime (Mirvish et al. 1982) and cyclopentanone oxime (Fiala et al. 1995) led in male rats to an increased incidence of liver tumours. The carcinogenicity is probably the result of the oxidation of the ketoximes to form the corresponding secondary nitroalkanes, as hepatocarcinogenic effects have been demonstrated also for the oxidation product of butanone oxime, 2-nitrobutane (Fiala et al. 1995), for the oxidation product of acetone oxime, 2-nitroproρane (Coulston 1983; Fiala et al. 1987; Lewis et al. 1979) and for 3-nitropentane (Fiala et al. 1995). As in the case of butanone oxime, the hepatocarcinogenic effects of acetone oxime (Mirvish et al. 1982) and 2-nitropropane (Coulston 1983) were more severe in male rats than in females.

It has been suggested that also the DNA-damaging effects of the ketoximes result from *in vivo* oxidation to the corresponding secondary nitroalkanes (Fiala et al. 1995; Hussain et al. 1990); Mirvish et al. 1982, which are metabolized in the liver in a sulfotransferase-dependent reaction to form a reactive, DNA-binding species.

3 Toxicokinetics and Metabolism

In male and pregnant female mice, the absorption and distribution of [^{14}C]butanone oxime was determined by means of whole animal autoradiography 20 minutes and 1, 3, 9 and 24 hours after oral and intratracheal administration. Butanone

oxime was rapidly absorbed after both administration routes. High concentrations in tissue were detected in the liver and nasal epithelium independent of the route of absorption. In addition, increased radioactivity was found in bone marrow, the spleen, salivary glands, Harderian gland, intestinal wall, mammary glands and pancreas.

In the foetuses, the highest concentrations in tissue were found in the liver; 24 hours after administration the foetal tissue levels were higher than those in the dams. A high level of radioactivity was detected in urine, while in the contents of the intestine there was only minimal radioactivity (Allied 1981).

The data for the acute toxicity of butanone oxime in rabbits (see Section 5.1.3) indicate percutaneous absorption.

There are no studies available of the metabolism of butanone oxime in animals and humans. It must, however, be assumed that butanone oxime is hydrolysed in the organism to form butanone and hydroxylamine. The findings described in Section 5.6.2 (Genotoxicity *in vivo*) regarding the formation of modified nucleosides by butanone oxime and structurally related ketoximes, indicate that there is another metabolic pathway for the ketoximes investigated which is connected with their genotoxic effects. It has been suggested that the DNA-damaging effects of the ketoximes result from their *in vivo* oxidation to form the corresponding secondary nitroalkanes (Fiala et al. 1995; Hussain et al. 1990; Mirvish et al. 1982). Oxidation of acetone oxime—albeit very slight—to form propane-2-nitronate, the anion of 2-nitropropane, has been demonstrated in liver microsomes of the rat, mouse and humans (Kohl et al. 1992). The anionic form of the nitroalkanes is apparently transformed by a sulfotransferase—which is expressed in the liver of male animals with a higher level of activity than in the liver of female animals—with simultaneous reduction to the corresponding ketone and hydroxylamine-*O*-sulfonic acid. The spontaneous degradation of hydroxylamine-*O*-sulfonic acid leads to the formation of a nitrenium ion, which is probably responsible for the formation of the aminated base 8-aminoguanine in the DNA and RNA (Sodum et al. 1993, 1994).

2-Nitropropane induces in rat hepatocytes, and to a much smaller extent in mouse and human hepatocytes, DNA repair synthesis (Davies et al. 1993). It must, therefore, be assumed that the enzymes responsible for the activation of secondary nitroalkanes and ketoximes are expressed also in human cells. It is, however, still unclear whether, and to what extent, this leads in humans under relevant exposure conditions to the metabolism of butanone oxime via nitrobutane.

4 Effects in Humans

In humans, 24-hour exposure of the forearm to butanone oxime did not cause irritation (Bayer 1969).

According to a producer of butanone oxime, no evidence of skin sensitization in humans is known (Allied 1983 b). Nor have any cases of skin sensitization been published since this memorandum.

5 Animal Studies

5.1 Acute toxicity

Data for the acute toxicity of butanone oxime are shown in Table 1.

5.1.1 Inhalation

In the available studies, butanone oxime was found to be of low acute toxicity in rats, with LC_{50} values of about 5000 ml/m³. Typical symptoms of intoxication were agitation (Kurita 1967) followed by lethargy and sedation, which occurred after concentrations of about 700 ml/m³ and above (Bayer 1969). After concentrations of 400 ml/m³ and above (1450 mg/m³; 4-hour exposure), increased methaemoglobin values were described (Allied 1991).

In time saturation tests with rats, mortality was not observed after 4-hour exposure to vapour generated at 25°C and 100°C (Dow Corning 1963) or 8-hour exposure (no other details) (Servo Delden 1995).

Table 1 Acute toxicity of butanone oxime

Administration	Species	Concentration/dose	Effects	References
inhalation	Rat	711 ml/m³ (4 hours)*	no deaths (sedative effect)	Bayer (1969)
		823 ml/m³ (4 hours)#	no deaths (reduced general well-being)	
		2500 ml/m³ (4 hours) 5000 ml/m³ (4 hours) 10000 ml/m³ (4 hours)	mortality 0/4 mortality 3/4 mortality 4/4	DuPont 1965
		about 5500 ml/m³ (4 hours)	LC_{50}	Servo Delden 1995
inhalation	rabbit, mouse, guinea pig	823 ml/m³ (4 hours)#	no deaths	Bayer (1969)
oral	rat	♂ 930 mg/kg body weight ♀ 1620 mg/kg body weight	LD_{50}	Mooney Chem 1982
		2300–3700 mg/kg body weight	LD_{50}	Allied 1983 b
		2326 mg/kg body weight	LD_{50}	Allied 1978 a
		about 2500 mg/kg body weight	LD_{50}	Bayer (1969)

Table 1 (Continued)

Administration	Species	Concentration/dose	Effects	References
		2528 mg/kg body weight	LD_{50}	Servo Delden 1995
		about 3700 mg/kg body weight (about 4 ml/kg body weight)	LD_{50}	Allied 1958
	mouse	1000 mg/kg body weight	mortality 1/15	Bayer (1969)
		1000 mg/kg body weight	LD_{50}	Allied 1983 b
dermal	rat	500 mg/kg body weight	no mortality	Bayer (1969)
intraperitoneal	mouse	521 mg/kg body weight	LD_{50}	Servo Delden 1995
	mouse	200 mg/kg body weight	LD_{50}	Sax and Lewis 1989
subcutaneous	rat	2700 mg/kg body weight	LD_{50}	Kurita 1967
	rat	2762–2813 mg/kg body weight	LD_{50}	Kurita 1967

* dynamic spray inhalation, analysed concentration
\# static spray inhalation, analysed concentration

5.1.2 Ingestion

The acute oral toxicity of butanone oxime is low, with LD_{50} values of usually > 2000 mg/kg body weight in the rat and ≥ 1000 mg/kg body weight in the mouse. After oral administration, well-being was impaired in the rat and mouse, and sedative effects with reduced motor activity were observed (Bayer 1969; IHF 1991 a, b; Schulze and Derelanko 1993). The symptoms usually disappeared after 2 to 5 days (Bayer 1969). Autopsy did not yield any substance-related findings (Bayer 1969; Mooney Chem 1982).

5.1.3 Dermal absorption

After dermal absorption, the LD_{50} for the rabbit was found to be between 0.2 and 2 ml/kg body weight (corresponding to 184 and 1840 mg/kg body weight). The 2 ml/kg body weight dose was lethal in all rabbits. Narcosis was the dominant symptom of intoxication. Methaemoglobin formation was observed after 0.2 and 2 ml/kg body weight, and there was an increase in the reticulocyte count after 0.2 ml/kg body weight (no other details) (Allied 1991).

In the rat, dermal application of 500 mg/kg body weight did not lead to symptoms of intoxication. No local effects on the treated areas of skin were observed (Bayer 1969).

5.2 Subacute, subchronic and chronic toxicity

The results of toxicity studies with repeated exposure are summarized in Table 2.

Table 2 The toxicity of butanone oxime after repeated administration

Species	Concentration/dose	Effects	References
rat, ChR-CD groups of 6 ♂	inhalation 10 days (4 hours/day) 0, 220 ml/m³	220 ml/m³: slight hyperaemia and effects on respiration	DuPont 1966
rat, strain not stated groups of 10	inhalation 10 days (2 hours/day) 0, 4 ml/kg body weight sprayed	4 ml/kg: narcosis, reversible within one hour	Allied 1958
rat, strain not stated groups of 10 ♂, 10 ♀	inhalation 4 weeks (6 hours/day, 5 days/week) 0, 60, 283, 533, 714 ml/m³	up to 283 ml/m³: no effects (no data given for olfactory epithelium) 533 ml/m³ and above: brain and spleen weights changed, effects on blood count and clinico-chemical parameters 714 ml/m³: haemosiderosis in the spleen, effects on the brain and spleen tissue	Dow Corning 1983
rat, F344 groups of 10 ♂, 10 ♀	inhalation 4 weeks (6 hours/day, 5 days/week) 0, 25, 100, 400 ml/m³	25 ml/m³: no effects (no data given for olfactory epithelium) 100 ml/m³ and above: MetHb increased (♀) 400 ml/m³: liver weights increased, spleen weights increased, MetHb increased, reticulocyte count increased, thrombocyte count increased, leukocyte count increased, MCH increased, MCV increased, Hb decreased, HC decreased, erythrocyte count decreased, MCHC decreased	IHF 1990 f

Table 2 (Continued)

Species	Concentration/dose	Effects	References
rat, F344 groups of 10 ♂, 10 ♀	inhalation 8 weeks (6 hours/day, 5 days/week) 0, 1000 ml/m³	1000 ml/m³: mortality increased, activity decreased, exhaustion, spleen weights increased, liver weights increased, adrenal gland weights increased, other organ weights increased, MetHb increased, anaemia, thrombocyte count increased, reticulocyte count increased, leukocyte count increased	IHF 1991 e
rat, F344 groups of 80 ♂, 80 ♀	inhalation 26 months (6 hours/day, 5 days/week) 0, 15, 75, 375 ml/m³ whole animal exposure	15 ml/m³ and above: degeneration of the olfactory epithelium, liver toxicity (♂), liver adenomas not significantly increased (2/80 ♂), congestion in the spleen 75 ml/m³ and above: size of testes increased, liver adenomas increased (♂) 375 ml/m³: body weights increased, liver toxicity, corneal clouding, liver weights increased, spleen weights increased, testis weights increased, liver carcinomas increased (♂), Hb decreased, erythrocyte count decreased, thrombocyte count increased	IHF 1993 a
mouse, CD-1 groups of 10 ♂, 10 ♀	inhalation 4 weeks (6 hours/day, 5 days/week) 0, 25, 100, 400 ml/m³	up to 100 ml/m³: no effects (no data given for olfactory epithelium) 400 ml/m³: spleen weights increased (♂), adrenal gland weights increased (♂), MetHb increased	IHF 1990 f
mouse, CD-1 groups of 10 ♂, 10 ♀	inhalation 8 weeks (6 hours/day, 5 days/week) 0, 1000 ml/m³	1000 ml/m³: mortality increased, activity decreased, exhaustion, spleen weights increased, liver weights increased, adrenal gland weights increased, other organ weights increased, MetHb increased, anaemia, thrombocyte count increased, reticulocyte count increased, leukocyte count increased	IHF 1991 e

Table 2 (Continued)

Species	Concentration/dose	Effects	References
mouse, CD-1 groups of 5–10 ♂	inhalation 13 weeks (6 hours/day, 5 days/week) 0, 3, 10, 30, 100 ml/m³	3 ml/m³: no effects (NOEC) 10 ml/m³ and above: minimal effects on the olfactory epithelium (reversible) 30 ml/m³ and above: effects on the olfactory epithelium (not reversible)	IHF 1995 a
mouse, CD-1 groups of 60 ♂, 60 ♀	inhalation 18 months (6 hours/day, 5 days/week) 0, 15, 75, 375 ml/m³ whole body exposure	15 ml/m³ and above: degeneration of the olfactory epithelium, liver toxicity (♂), liver adenomas not significantly increased (♂) 375 ml/m³ and above: liver carcinomas increased (♂), MetHb increased (♂), creatinine increased (♂), protein increased (♂)	IHF 1993 b
rat, SD groups of 6 ♀[1)]	oral (gavage) days 6–15 of gestation 0, 25, 100, 200, 400, 500, 625, 750 mg/kg body weight and day	25 mg/kg and above: MetHb increased, reticulocyte count increased 100 mg/kg and above: spleen size increased 400 mg/kg and above: clinical symptoms 625 mg/kg and above: body weights decreased	IHF 1990 a
rat, F344 groups of 15 ♀	oral (gavage) 28 days 0, 250, 500 mg/kg body weight and day	250 mg/kg and above: liver weights increased, extramedullary haematopoiesis (liver), liver cell hypertrophy	Allied 1995
rat, strain not stated groups of 25 ♂, 25 ♀	oral (probably gavage) 13 weeks 0, 25, 75, 225 mg/kg body weight and day	25 mg/kg and above: spleen size increased, spleen weights increased, liver weights increased, kidney weights increased, extramedullary haematopoiesis and pigments in the spleen and liver, congestion in the spleen, anaemia, slight effects on the leukocytes	

Table 2 (Continued)

Species	Concentration/dose	Effects	References
		75 mg/kg and above: biochemical effects, pigments in the kidneys, HC decreased, Hb decreased, erythrocyte count decreased, Heinz inclusion bodies increased, reticulocyte count increased 225 mg/kg and above: body weights decreased (♂)	Allied 1977
rat, SD groups of 10 ♂, 10 ♀	oral (gavage) 13 weeks (5 days/week) 0, 40, 125, 400 mg/kg body weight and day	40 mg/kg and above: MCV decreased, MetHb increased, Heinz inclusion bodies increased, leukocyte count increased, spleen size increased (♂) 125 mg/kg and above: spleen size increased, absolute liver weights increased (♀) 400 mg/kg and above: pallor, ataxia, activity decreased, salivation, dark urine, liver weights increased	IHF 1991 c; Schulze and Derelanko 1993
rat, SD groups of 30 ♂, 30 ♀	oral (gavage) 2 generations 0, 10, 100, 200 mg/kg body weight and day 5 days/week, for at least 10 weeks until mating, then 7 days/week, 3 weeks (♂) and 8 weeks (♀)	10 mg/kg and above: haematopoiesis and pigments in the spleen and liver, congestion in the spleen, changes in the testes, anaemia 100 mg/kg and above: body weights decreased (♂), spleen weights increased (♂), reticulocyte count increased, MetHb increased (♂), MCV increased, MCH increased, leukocyte count increased 200 mg/kg and above: mortality increased, body weights decreased (F_0), MCHC decreased	IHF 1992; Tyl et al. 1996
rat, strain not stated groups of 5 ♂, 5 ♀	oral 372 days 0.4 ml/kg body weight with the drinking water	0.4 ml/kg: in 1/10 animals spleen size increased	Allied 1958
rabbit, NZW groups of 5 ♀[1)]	oral (gavage) days 6–18 of gestation 0, 10, 20, 40, 80 mg/kg body weight and day	10 mg/kg and above: MetHb increased, reticulocyte count increased 40 mg/kg and above: mortality increased, clinical symptoms, body weights decreased	IHF 1990 a

Table 2 (Continued)

Species	Concentration/dose	Effects	References
rat, strain not stated groups of 6 ♂	subcutaneous weeks 0, 92, 458, 915 mg/kg body weight and day	92 mg/kg and above: food consumption decreased, body weights decreased, spleen weights increased, Hb decreased 458 mg/kg and above: narcosis, liver weights increased, lymphopoenia in the spleen, inflammatory changes in the lungs, erythrocyte count decreased, leukocyte count decreased 915 mg/kg: further organ weight changes, lymphocyte count decreased	Kurita 1967
rat, strain not stated groups of 5 ♂	subcutaneous 4 weeks (every 2nd day) 0, 1373 mg/kg body weight and day	1373 mg/kg: cholinesterase activity in plasma and erythrocytes decreased	Kurita 1967

[1)] mostly pregnant animals
Hb: haemoglobin; MCHC: mean corpuscular haemoglobin concentration; HC: haematocrit; MCH: mean corpuscular haemoglobin; F344: Fischer 344 rat; MCV: mean corpuscular volume; MetHb: methaemoglobin; NZW: New Zealand White; SD: Sprague Dawley

5.2.1 Inhalation

After inhalation exposure for 4 weeks, the formation of methaemoglobin was observed in rats after concentrations of 100 ml/m³ and above, and in mice after 400 ml/m³. The NOEC (no observed effects concentration) was about 25 and 100 ml/m³, respectively (IHF 1990 f). In the course of a long-term inhalation study, tolerance and adaptation were seen in rats. If methaemoglobin formation occurred after exposure to 375 ml/m³ for 3 months, this was no longer observed after 26 months (IHF 1993 a). Connected with the formation of methaemoglobin are also the increased spleen weights and extramedullary haematopoiesis observed in rats and mice after concentrations of 375 ml/m³ and above (IHF 1990 f, 1991 e, 1993 a, b).

Degeneration of the olfactory epithelium was observed in rats after exposure for 26 months and in mice after exposure for 18 months even at the lowest tested concentration of 15 ml/m³ (IHF 1993 a, b). To clarify the reversibility of the effects on the olfactory epithelium, a study was carried out with mice with inhalation exposure for 1, 2, 4 or 13 weeks, and for each of these exposure periods with recovery groups of 4 or 13 weeks. Concentrations of 0, 3, 10, 30 and 100 ml/m³ were inves-

tigated. After an exposure period of 1, 2 or 4 weeks, the NOEC was found to be 10 ml/m³; after exposure for 13 weeks it was 3 ml/m³. The effects on the olfactory epithelium were found to be reversible, but after concentrations of 30 ml/m³ and exposure and recovery for 13 weeks not completely so. After 100 ml/m³ the effects were not reversible after an exposure period of 1 or 13 weeks, even after a recovery period of 13 weeks (IHF 1995 a).

In addition to the local effects on the olfactory epithelium, liver toxicity was observed in male mice and rats after long-term exposure at the lowest concentration of 15 ml/m³, and liver adenomas and carcinomas after higher concentrations (see Section 5.7.2). In female animals there was evidence of liver toxicity only after higher concentrations (IHF 1993 a, b).

In addition, after long-term exposure to butanone oxime concentrations of 375 ml/m³, corneal clouding was observed in rats (IHF 1993 a).

5.2.2 Ingestion

The toxicity after repeated oral doses of butanone oxime is determined in rats and rabbits by the formation of methaemoglobin and the associated erythrocyte-damaging potential of the substance (Allied 1958, 1977, 1995; IHF 1990 a, 1991 c; Schulze and Derelanko 1993; Tyl et al. 1996). Also the increase in spleen size, spleen pigmentation and extramedullary haematopoiesis in the liver are connected with this. In a 2-generation study with rats, these effects occurred even at the lowest dose of 10 mg/kg body weight. Clinical symptoms seen after high doses were hypoactivity, ataxia and salivation (see Section 5.8) (IHF 1991 c; Schulze and Derelanko 1993).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Undiluted butanone oxime applied semi-occlusively or occlusively for 24 hours to the flanks or ears of rabbits was found to be non-irritative to moderately irritative (Allied 1978 c; Bayer 1969; Dow Corning 1963; Servo Delden 1995). On scarified skin, butanone oxime causes slight to severe irritation (Allied 1978 c; Dow Chem Corp 1968).

In an inadequately documented study of local tolerance in the rat, daily dermal application of the substance in petrolatum (concentration unknown) for 5 weeks led to reddening on day 4 of treatment, to blisters and local erosion on days 6 and 7, and to scab formation on day 10. After 15 days, slight hypertrophy of the corneal layer of the skin was still apparent (no other details) (Kurita 1967). Eight non-occlusive applications of the undiluted test substance to the ear did not cause any effects on the skin, however (Dow Chem Corp 1968).

5.3.2 Eyes

In the eye, butanone oxime leads to severe local irritative effects such as reddening of the eyelids and conjunctiva, and to corneal damage (Dow Chem Corp 1968; Kurita 1967) and even corrosion (Allied 1978 b; Dow Corning 1963).

5.4 Allergenic effects

Studies with animals of the skin sensitizing effects of butanone oxime are shown in Table 3.

In the maximization test with guinea pigs, butanone oxime had marked skin sensitizing effects (Allied 1983 a; Gad et al. 1986). The results of an inadequately documented Buehler test were regarded as positive (Allied 1983 b); a modified Buehler test, with nine dermal applications during the induction phase, yielded

Table 3 Studies of the skin sensitizing effects of butanone oxime

Test system		Vehicle	Induction	Challenge	Result	References
skin hypersensitivity test	guinea pig, 8 animals (test group), 9 animals (vehicle group)	arachis oil	not specified	0.1% subcutaneous	questionably positive	Allied 1978 d
maximization test	guinea pig, groups of 10 animals (test, vehicle, positive group)	propylene glycol	3% intradermal, 100% dermal	50% dermal	positive (9/10)	Allied 1983 a; Gad et al. 1986; Gad 1988
Buehler test	guinea pig, (no other details)				questionably positive	Allied 1983 b
modified Buehler test	guinea pig, groups of 10 animals (test, positive group) and 5 animals (vehicle group)	propylene glycol	25% dermal (1 × 24 hours, 8 × 6 hours)	1) 5% dermal, 2) 5% dermal	positive (7/10) positive (9/10)	Allied 1989
mouse ear swelling test	mouse, 10 animals (test group), 5 animals (vehicle group)	70% ethanol	50% dermal	50% dermal	positive (4/10)	Gad et al. 1986; Gad 1988

positive results (Allied 1989). Also a mouse ear swelling test confirmed the allergenic effects of butanone oxime on the skin (Gad et al. 1986).

5.5 Reproductive toxicity

The reproductive toxicity studies are listed in Table 4.

Table 4 The reproductive toxicity of butanone oxime

Species	Dose	Effects	References
rat, SD groups of 6 ♀	oral (gavage) days 6–15 of gestation 0, 25, 100, 200, 400, 500, 625, 750 mg/kg body weight and day	25 mg/kg and above: F_0: MetHb increased, reticulocyte count increased 100 mg/kg and above: F_0: size of spleen increased 400 mg/kg and above: F_0: clinical symptoms 625 mg/kg and above: F_0: body weights decreased; F_1: no substance-related findings 750 mg/kg: F_1: foetal body weights decreased	IHF 1990 a
rat, SD groups of 25 ♀	oral (gavage) days 6–15 of gestation 0, 60, 200, 600 mg/kg body weight and day	60 mg/kg and above: F_0: spleen size increased 200 mg/kg and above: F_0: clinical symptoms, body weights decreased up to 600 mg/kg: F_1: no substance-related findings	IHF 1990 b; Mercieca et al. 1991
rat, SD groups of 30 ♂, 30 ♀	oral (gavage) 2 generations 0, 10, 100, 200 mg/kg body weight and day 5 days/week, for at least 10 weeks until mating, then 7 days/week, 3 weeks (♂) and 8 weeks (♀)	10 mg/kg and above: parent animals: extramedullary haematopoiesis and haemosiderosis in the spleen and liver, anaemia 100 mg/kg and above: parent animals: clinical symptoms, body weights decreased, spleen weights increased, erythrocyte count decreased, reticulocyte count increased, MCV increased, MCHC increased, MetHb increased (♂), leukocyte count increased 200 mg/kg: parent animals: mortality increased; offspring: no substance-related findings	IHF 1992; Tyl et al. 1996
rabbit, NZW groups of 5 ♀	oral (gavage) days 6–18 of gestation 0, 10, 20, 40, 80 mg/kg body weight and day	10 mg/kg and above: F_0: MetHb increased, reticulocyte count increased up to 20 mg/kg: F_1: no substance-related findings	

Table 4 (Continued)

Species	Dose	Effects	References
		40 mg/kg and above: F_0: mortality increased, clinical symptoms, body weights decreased; F_1: no substance-related findings, incidence of spontaneous abortions increased (1/5)	IHF 1990 c
rabbit, NZW groups of 18 ♀	oral (gavage) days 6–18 of gestation 0, 8, 14, 24, 40 mg/kg body weight and day	up to 14 mg/kg: F_0: no substance-related findings (haematological parameters not determined) 24 mg/kg and above: F_0: food consumption decreased; F_1: no substance-related findings 40 mg/kg: F_0: mortality increased (8/18), body weights decreased, clinical symptoms; F_1: incidence of spontaneous abortions increased (3/18)	IHF 1990 d; Mercieca et al. 1991

MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; MetHb: methaemoglobin; NZW: New Zealand White; SD: Sprague Dawley

There was no evidence of embryotoxic effects after oral doses of up to 600 mg/kg body weight and day in the rat (IHF 1990 a, b; Mercieca et al. 1991) and up to 20 mg/kg body weight and day in the rabbit (IHF 1990 c, 1990 d); Mercieca et al. 1991. Foetotoxic effects (spontaneous abortions, reduced foetal weights) were observed at maternally toxic doses of 750 mg/kg body weight and day in rats and of 40 mg/kg body weight and day in rabbits. There was no evidence of teratogenic effects (IHF 1990 a, c, d; Mercieca et al. 1991).

A 2-generation study with rats did not yield any evidence of an impairment in fertility or of postnatal toxicity up to the highest administered dose of 200 mg/kg body weight and day, which was toxic for the parent animals (increased mortality, clinical symptoms, anaemia, reduced body weight gains) (IHF 1992; Tyl et al. 1996).

5.6 Genotoxicity

5.6.1 In vitro

The available studies of the genotoxicity of butanone oxime *in vitro* summarized in Table 5 yielded mainly negative results. Butanone oxime was not found to be mutagenic in various *Salmonella typhimurium* strains either in the presence or absence of an exogenous metabolic system (S9 fraction from the livers of rats and ham-

Table 5 The genotoxicity of butanone oxime *in vitro*

Test system		Concentration	Result		References
			without S9	with S9	
SMT	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10–10000 µg/plate	–	–(R, H)	NCI 1985 b
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	5–5000 µg/plate	–	–(R)	Allied 1975
	Salmonella typhimurium TA98, TA100, TA1535, TA1537	100–10000 µg/plate		–(R, H)	Allied 1985
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA97	100–10000 µg/plate (preincubation)	–	–(R, H)	NTP 1997
	Salmonella typhimurium TA98, TA100, TA1535, TA1537	100–5000 µg/plate	–	–(R)	Allied 1983 d
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	100–10000 µg/plate	–	–(R,H)	Rogers-Back et al. 1988
	Salmonella typhimurium TA98, TA100, 2637, *Escherichia coli* WP2uvr	not specified	–	–	Araki et al. 1986
$TK^{+/-}$	mouse lymphoma cells (L5178Y/$TK^{+/-}$)	1.7–3.6 µl/ml	–	–(R)	NCI 1985 a; Rogers-Back et al. 1988
		4.6–6.5 µl/ml	+ *	–(R)	
SCE	CHO cells	0.03–1% v/v	–	–(R)	Allied 1983 c
SCE	CHO cells	17–497 µg/ml	–	–(R)	NTP 1997
CA	CHO cells	745–14900 µg/ml	–	–(R)	NTP 1997
UDS	primary rat hepatocytes	0.15–1500 µg/ml	–		IHF 1995 b

* Concentrations cytotoxic
CA: chromosomal aberrations; (H): S9 mix from the hamster; (R): S9 mix from the rat; SCE: sister chromatid exchange; SMT: *Salmonella* mutagenicity test; UDS: unscheduled DNA synthesis (DNA repair synthesis)

sters). Studies with the *Escherichia coli* strain WP2uvr also yielded no evidence of mutagenic effects.

In ovary cells of the Chinese hamster (CHO cells), butanone oxime did not cause the induction of sister chromatid exchange (SCE) or chromosomal aberrations either in the presence or absence of S9 from rat liver. In primary rat hepatocytes, butanone oxime did not induce DNA repair synthesis.

In a mutation test with L5178Y/TK$^{+/-}$ mouse lymphoma cells, butanone oxime was found to be mutagenic in the clearly cytotoxic range (reduction in cell growth to 29% to 6% of that in untreated controls) in the absence of an exogenous metabolic system. No details were given about the type of induced mutant colonies. Butanone oxime was not mutagenic in the presence of rat liver S9, however.

The mainly negative findings for the genotoxicity of butanone oxime *in vitro* are in agreement with the observation that also for the homologous ketoxime acetone oxime—which leads in rat liver to the same DNA modifications and liver carcinomas as butanone oxime (see Section 5.6.2)—to date no genotoxic effects could be demonstrated *in vitro*. Acetone oxime induced neither DNA repair synthesis in V79 cells (Haas-Jobelius et al. 1991; Kreis 1996), primary ram seminal vesicle cells (Kreis 1996) and primary rat hepatocytes (Haas-Jobelius et al. 1991; Kreis 1996), nor mutations at the HPRT (hypoxanthine guanine phosphoribosyl transferase) locus in V79 cells (Haas-Jobelius et al. 1991), nor the formation of modified DNA nucleosides in ram seminal vesicle cells and primary rat hepatocytes (Kreis 1996).

The negative findings for the genotoxicity of butanone oxime in all of the *in vitro* test systems used are probably explained by the fact that the *N*-oxidation of the oxime to form the anion of 2-nitrobutane practically never takes place under *in vitro* conditions. In addition, in most non-hepatic cells, the liver-specific sulfotransferase form necessary for the activation of the anion is probably almost completely lacking.

5.6.2 In vivo

The available studies of the genotoxicity of butanone oxime *in vivo* are listed in Table 6.

In a test for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster*, there was no evidence of mutagenic effects caused by butanone oxime. In a micronucleus test with mice and a cytogenetic study with rat bone marrow, butanone oxime was not found to cause chromosomal damage.

After intraperitoneal administration of butanone oxime (2.24 mmol/kg body weight) to male F344 rats, the development of the DNA modification "DX1", the RNA modifications "RX1" and "RX2" and the increased formation of 8-oxoguanine in DNA and RNA were detected in the liver of the animals (Hussain et al. 1991). The modification RX2 has in the meantime been identified as 8-aminoguanosine (Sodum et al. 1993); the structures of the modifications DX1 and RX1 have not yet been clarified.

Table 6 The genotoxicity of butanone oxime *in vivo*

Test system		Dose	Result	References
SLRL	*Drosophila melanogaster*, ♂	oral, 3 days 7500 ppm with the diet	–	IHF 1991 d
CA, bone marrow	rat, Sprague Dawley, ♂, ♀	oral, one dose of 0, 300, 600 or 1200 mg/kg body weight	–	IHF 1990 e
MN, bone marrow, peripheral blood	mouse, no details	not specified	–	Servo Delden 1995
oxidative DNA/RNA changes, liver	rat, F344, ♂	intraperitoneal, one dose of 2.24 mg/kg body weight	+ [1)]	Hussain et al. 1991

[1)] (8-Hydroxydesoxyguanosine, 8-hydroxyguanosine and not identified modifications DX1 and RX1)
CA: chromosomal aberrations, MN: micronucleus test, SLRL: test for X-chromosomal recessive lethal mutation

The development of the nucleic acid modifications DX1 and 8-aminoguanosine and the increased formation of 8-oxoguanine in DNA and RNA were detected also after administration of the ketoximes acetone oxime (Guo et al. 1990; Hussain et al. 1990), 3-pentanone oxime, 4-heptanone oxime (Hussain et al. 1991), cyclopentanone oxime (Conaway et al. 1991) and cyclohexanone oxime (Hussain et al. 1991) and of the secondary nitroalkanes 2-nitropropane, 2-nitrobutane, 3-nitropentane, 2-nitroheptane, 2-nitrooctane and nitrocyclopentane (Conaway et al. 1991). The ketoximes were less effective than their oxidation products, the corresponding secondary nitroalkanes (Guo et al. 1990; Hussain et al. 1990). The DNA-modifying effects of both substance groups were stronger in male animals than in females (Guo et al. 1990). After an improvement in the HPLC analysis procedure for detecting modified nucleosides, it was shown that also 8-aminodesoxyguanosine is formed in the liver DNA of rats treated with 2-nitropropane (Kreis 1996; Sodum et al. 1993, 1994).

Overall, the findings described regarding the formation of modified nucleosides indicate that butanone oxime and all the other ketoximes and secondary nitroalkanes investigated to date lead to the same nucleic acid modifications in the liver, which suggests a common activation mechanism.

5.7 Carcinogenicity

5.7.1 Short-term studies

An inadequately documented data summary refers, without giving any details, to a cell transformation test with Syrian hamster cells with negative results (Allied 1983 b).

5.7.2 Long-term studies

In long-term inhalation studies with rats and mice given butanone oxime concentrations of 15, 75 and 375 ml/m³, an increase in the incidence of liver adenomas and liver carcinomas was found in the male animals (IHF 1993 a, b; see Table 7).

Table 7 The carcinogenicity of butanone oxime after inhalation exposure

Author:	IHF 1993 a
Substance:	butanone oxime (99.9%)
Species:	rat (F344), groups of 80 ♂, 80 ♀
Administration route:	inhalation (whole animal exposure)
Concentration:	0, 15, 75, 375 ml/m³ (determined analytically)
Duration:	26 months (6 hours/day, 5 days/week)
Toxicity:	15 ml/m³ and above: degeneration of the olfactory epithelium, liver toxicity (♂)
	375 ml/m³: body weights increased, survival unchanged, toxicity in various organs, extramedullary haematopoiesis, cataract formation, enzyme changes in blood in some cases
Tumours:	

Concentration (ml/m³)	0	15	75	375
liver adenomas	♂ 0/80 (0%)	2/80 (2.5%)	5/80 (6.3%)*	18/80 (22.5%)**
	♀ 0/80 (0%)	0/80 (0%)	2/80 (2.5%)	4/80 (5.0%)
liver carcinomas	♂ 0/80 (0%)	0/80 (0%)	1/80 (1.3%)	12/80 (15.0%)**
	♀ 0/80 (0%)	0/80 (0%)	0/80 (0%)	0/80 (0%)
mammary gland fibromas	♂ 2/80 (2.5%)	2/80 (2.5%)	4/80 (5.0%)	9/80 (11.3%)*
	♀ 10/80 (12.5%)	7/80 (8.8%)	9/80 (11.3%)	17/80 (21.3%)

Author:	IHF 1993 b
Substance:	butanone oxime (99.9%)
Species:	mouse (CD-1), groups of 60 ♂, 60 ♀
Administration route:	inhalation (whole animal exposure)
Concentration:	15, 75, 375 ml/m³ (determined analytically)
Duration:	18 months (6 hours/day, 5 days/week)
Toxicity:	15 ml/m³ and above: degeneration of the olfactory epithelium, liver toxicity (♂)
	375 ml/m³: survival unchanged, no clinical symptoms, after 12 and 18 months increased virus titre e.g. for hepatitis viruses
Tumours:	

Table 7 (Continued)

Concentration (ml/m³)		0	15	75	375
liver adenomas	♂	4/60 (6.7%)	11/60 (18.3%)	10/60 (16.7%)	11/60 (18.3%)
	♀	0/60 (0%)	0/60 (0%)	1/60 (1.7%)	3/60 (5.0%)
liver carcinomas	♂	2/60 (3.3%)	2/60 (3.3%)	1/60 (1.7%)	10/60 (16.7%)*
	♀	0/60 (0%)	0/60 (0%)	0/60 (0%)	1/60 (1.7%)

* $p < 0.05$; ** $p < 0.01$

In male rats, a significantly increased number of liver adenomas was observed after concentrations of 75 ml/m³ and above, and in male rats and mice, a significantly increased number of liver carcinomas after 375 ml/m³. At the end of the experiment there was evidence of liver cell damage and a trend towards increased liver adenomas even after 15 ml/m³ in male rats and mice. In the female animals, however, there was only a slight increase in the number of liver adenomas, which was not significant, in the two high concentration groups. In the male rats, but not the females, in addition a significant increase in the number of fibromas of the mammary gland was found after concentrations of 375 ml/m³. Survival of the animals was not significantly changed in any of the groups relative to that of the controls.

5.8 Other effects

5.8.1 Neurotoxicity

In a study of the acute neurotoxicity of butanone oxime, 4 rats per sex and group were given oral doses of 0 or 900 mg/kg body weight. Reduced motor activity was observed after 30 to 60 minutes (IHF 1991 a; Schulze and Derelanko 1993).

In another study of neurotoxicity after single oral doses, 10 rats per sex and group were given 0, 100, 300 or 900 mg/kg body weight. Mortality, body weights and food consumption were unchanged. After the 300 mg/kg body weight dose and above, a reversible reduction in motor activity was observed within 6 hours (IHF 1991 b; Schulze and Derelanko 1993). In rats given oral doses of 0, 40, 125 or 400 mg/kg body weight and day for 13 weeks (see Table 2), hypoactivity, ataxia and salivation were observed after 400 mg/kg body weight and day. There was, however, no evidence of irreversible or cumulative neurotoxic effects (IHF 1991 c; Schulze and Derelanko 1993).

6 Manifesto (MAK value/classification)

Inhalation exposure to butanone oxime leads in male rats and mice to liver carcinomas. The hepatocarcinogenicity is evidently a consequence of the induction of DNA modifications in the liver cells as the result of liver-specific enzymatic activation. At present it cannot be excluded that this activation can take place also in human liver. Butanone oxime is therefore listed in Section III, Category 2 of the *List of MAK and BAT Values*.

As a result of the allergenic effects on the skin demonstrated in animal studies, the substance is designated with an "Sh".

The data for the acute toxicity of butanone oxime in rabbits indicate percutaneous absorption. The substance is therefore designated with an "H".

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