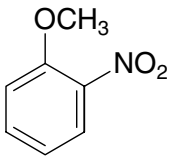
2-Nitroanisole

Classification/MAK value:	**see Section IIIA2 of the List of MAK and BAT Values**
MAK value dates from:	**1994**
Synonyms:	1-methoxy-2-nitrobenzene *o*-nitroanisole o-nitrophenyl methyl ether
Chemical name (CAS):	1-methoxy-2-nitrobenzene
CAS number:	91-23-6
Structural formula:	
Molecular formula:	$C_7H_7NO_3$
Molecular weight:	153.15
Melting point:	9.4–10.4°C
Boiling point:	150.5–151.0°C
Vapour pressure at 30°C:	0.04 hPa
Density at 20°C:	1.25 g/cm^3
1 ml/m^3 (ppm) = 6.35 mg/m^3	**1 mg/m^3 = 0.15 ml/m^3 (ppm)**

There is a BUA report available for 2-nitroanisole (BUA 1987).

1 Toxic Effects and Modes of Action

2-Nitroanisole is of low to moderate acute toxicity and after high single doses produces only non-specific toxic symptoms.

It does not irritate the skin or mucous membranes.

2-Nitroanisole is rapidly absorbed, metabolized and excreted mainly with the urine. The main route of metabolism is oxidative *O*-demethylation to *o*-nitrophenol, while reduction to *o*-anisidine is only a minor pathway.

After administration of relatively high concentrations for longer periods, the oxidative *O*-demethylation can become saturated and this can lead to increased reduction to *o*-anisidine.

After repeated oral administration (4 days and 28 days) the main effects are seen in the liver, blood count, spleen, kidneys and bladder. Subchronic exposure (13 weeks and 6 months) to 2-nitroanisole led to an increased incidence of tumours in the bladder, efferent urinary passages, large intestine and blood of rats, and to hepatocellular hypertrophy in mice.

In a long-term feeding study over 2 years, an increase in liver tumours was observed in mice and mononuclear leukaemia in rats.

Most *in vitro* tests for genotoxicity have yielded positive results with 2-nitroanisole. *In vivo* genotoxicity studies are not available.

At maternally toxic doses embryotoxic effects were observed, but no teratogenic effects.

There are no data available on the mechanisms of action of 2-nitroanisole.

2 Toxicokinetics

2-Nitroanisole is rapidly absorbed by the body, metabolized and excreted mainly with the urine.

After administration of the radioactive substance, the maximum level of radioactivity was reached in all target organs within 15 minutes. The highest levels of radioactivity were measured in muscle (20 %), skin (10 %), adipose tissue (6.8 %) and blood (6.5 %) (Miller *et al*. 1985).

Oxidative *O*-demethylation to *o*-nitrophenol is the most important route of metabolism of 2-nitroanisole, a further route is reduction to *o*-anisidine.

The urinary metabolites were investigated in the rat after intraperitoneal injection of a dose of 25 mg/kg body weight; 63 % of the administered dose was excreted in the form of *o*-nitrophenyl sulfate, 11 % as *o*-nitrophenyl glucuronide, 1.5 % as *o*-nitrophenol and 0.6 % as *o*-anisidine. About 24 % of the metabolites were not identified. The main route of degradation is therefore probably the oxidative *O*-demethylation to *o*-nitrophenol, while reduction to *o*-anisidine occurs to a lesser extent (Miller *et al*. 1985). It has been suggested that this route of metabolism becomes saturated after repeated administration of high doses, causing an increase in the formation of *o*-anisidine via nitroreduction (NTP 1993). The similarity of the findings of the stop exposure study with 2-nitroanisole administered to rats (increased incidence of hyperplasia and neoplasia of bladder and kidneys) and findings from long-term studies with *o*-anisidine support this hypothesis (see Section 4.6).

Elimination takes place in two phases. The first elimination phase occurs in all target organs investigated with a half-time of 1 to 2 hours, while the second phase is slower and takes 2.5–6.2 days, depending on the target organ. After intravenous injection of ^{14}C-labelled 2-nitroanisole doses of 25 mg/kg body weight, about 90 % of the radioactivity was eliminated by the rat within as little as 24 hours: 82 % with the urine and 7.5 % with the faeces. Elimination after intravenous administration was just as rapid as after oral administration of the same 2-nitroanisole doses. The rate of renal elimination becomes noticeably slower above a certain dose. After oral doses of ^{14}C-labelled 2-nitroanisole of 5, 50 or 500 mg/kg body weight, excretion of the 500 mg/kg dose was significantly slower than that of the other two doses. After 24 hours 73 % of the 5 mg/kg dose and 69 % of the 50 mg/kg dose was eliminated by the rat with the urine, but only 34 % of the 500 mg/kg dose. In the high dose group a further 37 % of the administered radioactivity was eliminated between 24 and 48 hours after administration, while in the low dose group only 1 % to 2 % was eliminated during this period. Afterwards the elimination rates were the same in all dose groups. Within 7 days 78 % to 85 % of the dose was eliminated in the urine and faeces (Miller *et al*. 1985).

3 Effects in Man

After an accident involving spillage of 2-nitroanisole at an industrial plant, a programme of biological monitoring was carried out with all employees involved in cleaning up the contaminated area. In the urine of the exposed persons (over 500 individual analyses) *o*-nitrophenol glucuronides and *o*-nitrophenol sulfates were detected. Neither free 2-nitroanisole nor *o*-anisidine were found. The concentrations correlated clearly with the duration of the work and level of exposure. After completion of the work the values rapidly decreased to below the detection limit. In addition, the methaemoglobin levels were determined in 50 workers involved in the cleaning up. All values were within the normal range (Hessisches Ministerium für Frauen, Arbeit und Sozialordnung 1993; Schuckmann and Mayer 1993).

Investigation of the genotoxic effects of 2-nitroanisole (DNA strand breaks) using the alkali elution method was carried out in 19 exposed workers involved in cleaning up after the accident and 20 non-exposed employees. No significant increase in DNA strand breaks was detected (Hessisches Ministerium für Frauen, Arbeit und Sozialordnung 1993; Schuckmann and Mayer 1993).

4 Effects on Animals

There are no data available on the effects of inhalation of 2-nitroanisole.

4.1 Acute toxicity

4.1.1 Ingestion

2-Nitroanisole was found to be moderately toxic with an oral LD_{50} of about 750 to 2000 mg/kg body weight (see Table 1).

In rats after a single toxic dose of 2-nitroanisole, non-specific symptoms of intoxication, such as crouching, prostration, retracted flanks, unsteady gait, irregular breathing, ruffled fur, partially closed eye-lids, reduced spontaneous activity, dazed behaviour, reduced reflexes and lacrimation were seen. Autopsy of the animals which died revealed slight reddening of the mucous membranes of the stomach or of the whole gastrointestinal tract and in some cases pale kidneys, dark coloration of the adrenal glands and reddish brown discoloration of the lungs (Hoechst 1985a).

Data on the acute toxicity of 2-nitroanisole are listed in Table 1.

Table 1. Acute toxicity of 2-nitroanisole

Species	Sex	Administration route	LD_{50} (mg/kg body weight)	References
rat	♂ + ♀	oral	874	Hoechst 1985a
rat	♂	oral	760	Reznichenko *et al.* 1986
rat	♀	oral	740	Reznichenko *et al.* 1986
rat	♂	oral	1000	Bayer 1986
rat	♀	oral	890	Bayer 1986
rat	not specified	oral	1980	Vasilenko and Zvezdai 1981
mouse	♀	oral	1300	Reznichenko *et al.* 1986
mouse	not specified	oral	1450	Vasilenko and Zvezdai 1981
rat	♂ + ♀	dermal	> 2000	Hoechst 1985b

Occlusive application of single doses of 2-nitroanisole of up to 2000 mg/kg body weight for 24 hours to determine the dermal LD_{50} led to no deaths in rats (Hoechst 1985b).

4.2 Subacute, subchronic and chronic toxicity

4.2.1 Ingestion

In a 14-day feeding study groups of 5 male and 5 female F344/N rats and $B6C3F_1$ mice received 0, 583, 1166, 2332, 4665 or 9330 ppm 2-nitroanisole in the diet (about 60, 120, 230, 470 or 930 mg/kg body weight) and 0, 250, 500, 1000, 2000 or 4000 ppm (about 37, 75, 150, 300 or 600 mg/kg body weight), respectively. In the male rats there were reductions in body weight gain from 4665 ppm. In addition, increased absolute liver weights were found at concentrations of 1166 ppm and more for the male rats and

583 ppm and more for the female rats. Body weight gain was also reduced in the mice, in the males from 250 ppm and in the females from 4000 ppm (NTP 1993). A no effect level (NOEL) was not determined.

Groups of 5 male and 5 female Wistar rats received by gavage 2-nitroanisole doses of 0, 1.6, 8, 40 or 200 mg/kg body weight, daily for 28 days. In none of the treated animals were effects on food consumption or body weight gain observed. Behaviour and general condition remained unaffected up to doses of 40 mg/kg body weight. After doses of 40 mg/kg body weight and more increased liver weights were found in the animals but no histological changes. In the highest dose group non-specific clinical symptoms and haematological changes in the form of slight haemolytic anaemia and increased spleen weights were observed. The NOEL was found to be 8 mg/kg body weight (Hoechst 1989).

Oral administration of 2-nitroanisole doses of 150 mg/kg body weight, 30 times to male rats (strain not specified) led to slight haemolytic anaemia and an increase in the relative liver, kidney and spleen weights (Reznichenko *et al*. 1986).

In a 13-week feeding study, groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice received 2-nitroanisole daily in the diet in concentrations of 0, 200, 600, 2000, 6000 or 18000 ppm (about 10, 30, 100, 300 or 900 mg/kg body weight) and 0, 60, 200, 600, 2000 or 6000 ppm (about 9, 30, 90, 300 or 900 mg/kg body weight), respectively. In the female rats the absolute liver weights were increased from 200 ppm and in the male rats the absolute kidney weights from 600 ppm. At concentrations of 6000 ppm and above a reduction in food consumption and body weight gain and an increase in the spleen weights, increased methaemoglobin levels, anaemia and hyperplasia of the transitional epithelium of the bladder and haemosiderin deposits in the spleen were observed in the rats. In the 18000 ppm group a bladder papilloma was found in one male rat and bladder carcinomas in 2 male and 3 female rats. In addition congestion in the spleen, hepatocellular hypertrophy and degeneration of the germinal epithelium and uterus atrophy were detected in this group.

In the male mice, a dose-dependent increase in hepatocellular hypertrophy was observed at concentrations of 200 ppm and above. The absolute and relative liver weights were significantly increased in female animals given concentrations of 600 ppm, and the relative liver weights increased in male and female animals given 2000 and 6000 ppm, respectively. In male and female animals, haemoglobin levels and packed cell volumes were reduced from 2000 and 6000 ppm, respectively. At 6000 ppm reductions in food consumption and body weight gain were also observed (NTP 1993).

4.3 Local effects on skin and mucous membranes

2-Nitroanisole (0.5 ml undiluted) was applied semiocclusively to the shaved, intact skin of the flanks of 6 New Zealand White rabbits for 4 hours and did not produce any irritation (Hoechst 1985c).

A dose of 0.1 ml 2-nitroanisole, dropped into the conjunctival sac of 6 rabbits, led after 1 hour to swelling and diffuse reddening of the conjunctiva and to slight lacrima-

tion. After 24 hours all signs of irritation had disappeared. The observation period lasted 4 days (Hoechst 1985d).

There are no data available on allergenic effects.

4.4 Reproductive and developmental toxicity

4.4.1 Fertility

In a 13-week study with rats, degeneration of the germinal epithelium and uterus atrophy were observed at the highest dose (see Section 4.2).

4.4.2 Developmental toxicity

Twenty pregnant Sprague-Dawley rats were given 2-nitroanisole doses of 20, 80 or 320 mg/kg body weight by gavage in sesame oil from day 6 to day 15 of gestation. Unspecific clinical symptoms and a reduction in food consumption were seen in the dams of the middle and high dose groups but without any effects on body weights.

In the 320 mg/kg body weight group a slight increase in resorptions (8.5 %, controls: 5.0 %) and mild embryotoxic effects (slight increase in visceral variations and fusions) were observed. Teratogenic effects did not occur. Thus, 20 mg/kg body weight had no effect on the dams and 80 mg/kg body weight no effect on the foetuses (Hoechst 1993).

4.5 Genotoxicity

The results of *in vitro* tests for genotoxic effects of 2-nitroanisole are listed in Table 2.

The *Salmonella* mutagenicity test (Ames test) yielded positive results with TA100 from concentrations of 333 µg/ml with metabolic activation and from concentrations of 666 µg/ml without metabolic activation. The results with TA1535 are contradictory. No mutagenicity was observed with the other strains. This indicates that 2-nitroanisole can induce base-pair substitution (Chiu *et al.* 1978; Haworth *et al.* 1983; Inoue *et al.* 1981; Kawai *et al.* 1987; NTP 1993; Shimizu and Yano 1986; Suzuki *et al.* 1983).

With L5178Y mouse lymphoma cells (NTP 1993), at concentrations of 0.15 µl/ml and above, 2-nitroanisole induced trifluorothymidine resistance via mutation at the thymidine kinase locus (no information on the size of the colonies), while in the HPRT test with V79 cells (a cell line derived from Chinese hamster lung cells) no effect was detected (Hoechst 1988a).

Table 2. Genotoxicity studies with 2-nitroanisole

Test	Organism	Dose or concentration	Result with S9 mix	without S9 mix	References	Comments
reversion test	*S. typhimurium* TA98, TA100	15.3, 153.15, 1531.5, 3063 µg/plate	not tested	+		Chiu *et al.* 1978
reversion test	*S. typhimurium* TA98, TA100	not stated	not tested	+		Inoue *et al.* 1981
reversion test	*S. typhimurium* TA98, TA100	250, 500, 1000, 2500 µg/plate	+	+		Kawai *et al.* 1987
reversion test	*S. typhimurium* TA98, TA100, TA1535, TA1538 TA1537	0.1, 0.5, 1, 5, 10 µl/plate	not tested	+	toxic from 10 µl/plate	Shimizu and Yano 1986
reversion test	*S. typhimurium* TA98, TA100, TA1535, TA1537	10, 33, 100, 166, 333, 666, 1000, 1200, 1500, 1666, 2150, 3333 µg/plate	+	+	toxic from 1200 µg/plate with S9 mix from variously induced animals (rat, hamster)	Haworth *et al.* 1983, NTP 1993
reversion test	*S. typhimurium* TA 98, TA 100	50, 100, 200, 300 µg/plate (with S9 mix and norharman), 100 µg/plate (without S9 mix)	+	-	mutagenic only with norharman	Suzuki *et al.* 1983
rec test	*B. subtilis* H17 (rec^+), M45 (rec^-)	0.5, 5 µl/plate	not tested	+		Shimizu and Yano 1986
HGPRT test	V79 cell line (Chinese hamster)	250, 500, 750, 1000, 1250 µg/ml	-	-		Hoechst 1988a
mouse lymphoma test	L5178Y cell line	0.0125, 0.025, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5 µl/ml	not tested	+	toxic from 0.4 µl/ml	NTP 1993

Table 2. continued

Test	Organism	Dose or concentration	Result with S9 mix	Result without S9 mix	Comments	References
chromosome analysis	V79 cell line (Chinese hamster)	100, 550, 1000 µg/ml (toxic as from 1531 µg/ml)	+	+	at 1000 µg/ml without S9 aberrations in about 10 % of metaphases 18 h after application (with S9 aberrations in 4 %)	Hoechst 1988b
chromosome analysis	CHO cell line (Chinese hamster)	216.3, 432.6, 618.0, 803.4 µg/ml (without S9) 519, 762, 1060 µg/ml (with S9)	+	-	at 1060 µg/ml aberrations in 49 % of cells	Galloway *et al.* 1987, NTP 1993
sister chromatid exchange (SCE)	CHO cell line (Chinese hamster)	12.3, 41.2, 123, 202, 251, 301, 350 µg/ml (without S9) 608, 811, 1010 µg/ml (with S9)	+	+	toxic from 350 µg/ml (without S9), SCE in about 40 % of cells	Galloway *et al.* 1987, NTP 1993

In addition in mammalian cells (V79, CHO) at concentrations of 1000 µg/ml and above, 2-nitroanisole caused chromosomal aberrations. In CHO cells 2-nitroanisole induced sister chromatid exchange at concentrations of 123 µg/ml and above without metabolic activation and at 608 µg/ml and above with metabolic activation (Galloway *et al*. 1987; Hoechst 1988b; NTP 1993).

There are no data available for genotoxicity *in vivo*.

4.6 Carcinogenicity

Groups of 60 male and 60 female F344/N rats received 6000 or 18000 ppm 2-nitroanisole in the diet (about 300 or 900 mg/kg body weight) for 27 weeks (see Table 3). After this the animals were fed for a further 77 weeks without added 2-nitroanisole and observed (stop exposure study). Reductions in body weight gain and high substance-related mortality were found. In the high dose group all the males had died by the 47th week and all the females by the 61st week. After 3 months a carcinoma of the transitional epithelium of the bladder was found in one male rat of the 18000 ppm group. By the end of the experiment in both dose groups the incidence of papillomas and particularly of carcinomas of the transitional epithelium of the bladder was significantly increased. In addition, in both dose groups there was an increase in benign and malignant neoplasms in the large intestine and efferent urinary passages and cell hyperplasia of the transitional epithelium of the bladder and efferent urinary passages (NTP 1993).

In a 2-year study groups of 60 male and 60 female F344/N rats and B6C3F_1 mice were fed daily with food containing 222, 666 or 2000 ppm 2-nitroanisole (about 10, 30 or 100 mg/kg body weight) for the rats and 666, 2000 or 6000 ppm 2-nitroanisole (about 100, 300 or 900 mg/kg body weight) for the mice (see Table 3). In the male rats the main effects were nephropathy and focal hyperplasia in the renal tubules and forestomach. An increase in the incidence of leukaemia was found in both sexes. In the male mice 2-nitroanisole led to an increase in the incidence of hepatocellular adenomas, carcinomas and hepatoblastomas. An increase in the incidence of hepatocellular adenomas was observed in the female mice (NTP 1993).

A similar dose-response relationship for the induction of neoplasms in the bladder and kidneys of rats was also found with *o*-anisidine (NTP 1978). There are no carcinogenicity studies available for *o*-nitrophenol, the metabolite from the main route of metabolism of 2-nitroanisole.

Table 3. Carcinogenicity studies with 2-nitroanisole

Author:	NTP 1993			
Substance:	2-nitroanisole, purity > 99 %			
Species:	rat, F344/N, 60 ♂ and 60 ♀; controls 60 ♂ and 60 ♀			
Administration:	in the diet			
Dose:	0, 6000, 18000 ppm (about 0, 300, 900 mg/kg body weight)			
Duration:	27 weeks, 77 weeks observation period			
Toxicity:	increased mortality (survival rate ♂: 13/60, 1/60, 0/60; ♀: 14/60, 4/60, 0/60); reduced body weight gains in all treated animals; cell hyperplasia in the bladder and the efferent urinary passages			
Tumours		**0 ppm**	**6000 ppm**	**18000 ppm**
bladder				
transitional epithelium				
papillomas	♂	0/59	9/59	1/60
	♀	0/58	2/59	1/60
carcinomas	♂	0/59	27/59	50/60
	♀	0/58	28/59	48/60
squamous epithelium				
papillomas	♂	0/59	0/59	4/60
	♀	0/58	0/59	4/60
carcinomas	♂	0/59	0/59	6/60
	♀	0/58	0/59	1/60
sarcomas	♂	0/59	2/59	9/60
	♀	0/58	2/59	14/60
large intestine				
polyps	♂	0/60	26/60	30/60
	♀	0/60	8/60	18/60
carcinomas	♂	0/60	0/60	5/60
	♀	0/60	0/60	2/60
efferent urinary passages				
transitional epithelium				
papillomas	♂	0/60	0/60	4/60
	♀	0/60	0/60	1/60
carcinomas	♂	0/60	1/60	8/60
	♀	0/60	0/60	1/60

Author:	NTP 1993				
Substance:	2-nitroanisole, purity > 99 %				
Species:	rat, F344/N, 60 ♂ and 60 ♀; controls: 60 ♂ and 60 ♀				
Administration:	in the diet				
Dose:	0, 222, 666, 2000 ppm (about 0, 10, 30 or 100 mg/kg body weight)				
Duration:	103 weeks exposure				
Toxicity:	increased mortality in ♂ (survival ♂: 32/50, 34/50, 24/50, 9/50; ♀: 33/50, 41/50, 26/50, 33/50); reduced body weight gains in the ♂ of the 2000 ppm group; focal hyperplasia in the forestomach of ♂ and ♀; nephropathy and focal hyperplasia in the renal tubules in the ♂				
Tumours		**0 ppm**	**222 ppm**	**666 ppm**	**2000 ppm**
leukaemia	♂	26/50	25/50	42/50	34/50
	♀	14/50	11/50	14/50	26/50

Table 3. continued

Author:	NTP 1993				
Substance:	2-nitroanisole, purity > 99 %				
Species:	mouse, B6C3F$_1$, 60 ♂ and 60 ♀; controls: 60 ♂ and 60 ♀				
Administration:	in the diet				
Dose:	0, 666, 2000, 6000 ppm (about 0, 100, 300, 900 mg/kg body weight)				
Duration:	103 weeks				
Toxicity:	no increase in mortality; reduced body weight gains in the treated animals				
Tumours		**0 ppm**	**666 ppm**	**2000 ppm**	**6000 ppm**
liver					
adenomas	♂	14/50	26/50	41/50	29/50
	♀	14/50	20/50	36/50	18/50
carcinomas	♂	7/50	12/50	11/50	7/50
hepatoblastomas	♂	0/50	3/50	17/50	9/50

5 Manifesto (MAK value, classification)

In most of the available *in vitro* tests, 2-nitroanisole proved to be genotoxic. There are no data available on the genotoxicity *in vivo*. The results of long-term studies indicate a carcinogenic effect for 2-nitroanisole in animal experiments, although the meaningfulness of these studies is limited by the excessive doses administered.

2-Nitroanisole is classified in Category IIIA2 in the "List of MAK and BAT Values".

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completed 30.05.1994