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**METILOX**  
**CAS N°: 6386-38-5**

**SIDS Initial Assessment Report**  
**for**  
**13<sup>th</sup> SIAM**  
**(Bern, 6-9 November 2001)**

**Chemical Name:** Metilox  
**CAS No:** 6386-38-5  
**Sponsor Country:** Switzerland (Ciba Specialty Chemicals Inc.)

**National SIDS Contact Point in Sponsor Country :**

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**History:**

Metilox is **NOT** an ICCA chemical.

The chemical has been assigned to Switzerland in phase 1 of the OECD HPVC Programme. It was discussed at several OECD meetings, i.e. at the 1<sup>st</sup> Review Meeting in 1990 the majority of delegations identified the lack of information on genotoxicity and reprotoxicity and supported the proposals that such tests should be undertaken. At the 1<sup>st</sup> SIAM in 1993 a chronic aquatic toxicity test was recommended as well. In the meantime the recommended tests have been performed by the sponsor company and the results included in the redrafted SIAR.

**Testing :**

No testing

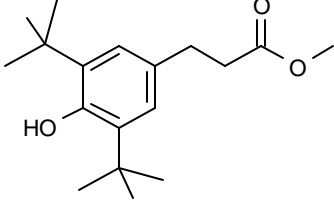
Testing  Water solubility  
Toxicity to algae  
Chronic toxicity to *Daphnia magna*  
Cytogenetic assay *in vitro*  
Reproduction/Developmental Toxicity

**Comments :**

**Deadline for circulation:** 14 September 2001

**Date of Circulation:** 28 September 2001

**SIDS INITIAL ASSESSMENT PROFILE**

<b>CAS No.</b>	6386-38-5
<b>Chemical Name</b>	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy -, methyl ester (Metilox)
<b>Structural Formula</b>	
<b>RECOMMENDATIONS</b> The chemical is currently of low priority for further work.	
<p><b>SUMMARY CONCLUSIONS OF THE SIAR</b></p> <p><b>Human Health</b></p> <p>Metilox was of low toxicity in acute toxicity tests, with an oral LD50 value of &gt;5000 mg/kg bw, an inhalation LC50 above 55 mg/m<sup>3</sup> and a dermal LD50 of &gt;3000 mg/kg. The substance is not irritating to the skin and eye. No indication for sensitisation due to Metilox was found.</p> <p>The LOAEL found after repeated oral exposure during a 90 day study was 70 mg/kg bw per day. The liver and thyroid were the target organs, showing hypertrophy. In a reproduction study the NOAEL for parental toxicity was 10 mg/kg bw per day, based on decreased food consumption, decreased body weight gain and liver hypertrophy. No effects on fertility were observed. Effects on pups (decreased litter size, viability and weight) were reported at 250 mg/kg bw per day. The NOAEL for developmental effects is 100 mg/kg bw per day. Metilox is not mutagenic in the Ames test and in the chromosome aberration test <i>in vitro</i>.</p> <p><b>Environment</b></p> <p>Metilox has a low vapour pressure and calculated logPow between 5 and 6. Water solubility is 2.2 mg/L. The substance is hydrolysed to its carboxylic acid. Both Metilox and its hydrolysis product are not or very limited biodegradable and are expected to end up in the sediment. In the 1970s Metilox and degradation products have been monitored in surface water and sediment near a contaminated production site.</p> <p>At the water solubility limit Metilox was not acutely toxic to fish and daphnids (96-h LC50 5.8 mg/L in fish and 24-h EC50 &gt;100 mg/L in a Daphnia test with the use of a dispersant (nominal concentrations)). For algal growth the 48 h EC50 was 2.3 mg/L (measured concentration). The NOEC in a <i>Daphnia magna</i> reproduction study was 0.123 mg/L. Based on this lowest NOEC and applying a safety factor of 50, a PNEC of 2.5 µg/L was derived.</p> <p>The BCF for the main metabolite, Metilox acid, has been determined in carp to be 60-223 (at 50 µg/L) and 121-532 (at 5 µg/L).</p> <p><b>Exposure</b></p> <p>The production volume of Metilox was 23,500 tonnes in 1992. Greater than 99.8% of the production volume is used as an intermediate in the synthesis of phenolic antioxidants for polymers. Other usages are as an antioxidant in motor oils, hydraulic fluids and lubricants. A very minor part of the production volume is used in fragrances.</p> <p>During production worker exposure is expected to be very low or negligible, due to the closed production process. Environmental exposure due to release via waste water during cleaning processes and spillage of motor oils may occur.</p> <p>Some consumers may be exposed to very low concentrations of Metilox found in fragrances.</p>	

**NATURE OF FURTHER WORK RECOMMENDED**

There is currently no concern for health.

Based on the available data there is currently no concern for the environment. However local, regional or national exposure information gathering may be considered. If that information indicates significant sediment exposure then the hydrolysis rate of Metilox and effects of Metilox and/or degradation products on sediment dwelling organisms should be investigated.

## FULL SIDS SUMMARY

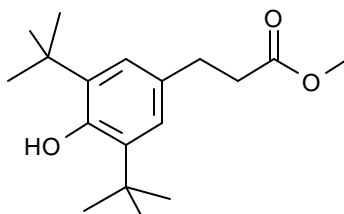
CAS-NO.: 6386-38-5		SPECIES	PROTOCOL	RESULTS
<b>PHYSICAL CHEMICAL</b>				
2.1	Melting Point		Ciba	66.1 °C
2.2	Boiling Point		Ciba	335.8 °C
2.3	Density		Ciba	1.09 g/cm <sup>3</sup> (64 °C)
2.4	Vapour Pressure		Ciba (thermo-gravimetry)	0.00002 hPa (25 °C)
2.5	Partition Coefficient (Log Pow)		Calculation	5.5-5.9
2.6 A	Water solubility		EEC 84/449 A6	2.2 mg/L
B	pH		Ciba	5.8
	pKa		-	-
2.12	Oxidation : Reduction potential		-	-
<b>ENVIRONMENTAL FATE / BIODEGRADATION</b>				
3.1.1	Photodegradation in air		Calculation	T1/2 = 19.7 hours
3.1.2	Stability in water		Monitoring data	Hydrolysis is expected
3.2	Monitoring data		-	Concentration in waste water 0.6-11 mg/L, surface water 0.025 mg/L sediment 1.5-170 mg/kg
3.3	Transport and Distribution		EQC model	air/soil/water/sedim: 8.5/8.4/2.2/89%,
3.5	Biodegradation		EEC 84/449 C5 (CO <sub>2</sub> evolution test)	Not biodegradable
<b>ECOTOXICOLOGY (lowest effect concentrations only)</b>				
4.1	Acute/prolonged toxicity to fish	<i>Brachydanio rerio</i>	OECD 203	LC <sub>50</sub> (96h) = 5.8 mg/L
4.2	Acute/prolonged toxicity to aquatic invertebrates (daphnia)	<i>Daphnia magna</i> Straus	OECD 202	EC <sub>50</sub> (24h) > 100 mg/L
4.3	Toxicity to aquatic plants e.g. algae	<i>Scenedesmus subspicatus</i>	EC, OJ L133/89; 30.4.1988	EC <sub>50</sub> (72h) = 2.3 mg/L
4.4	Toxicity to microorganisms	Waste water bacteria	OECD 209	EC <sub>50</sub> (3h) > 100 mg/L
4.5.2	Chronic toxicity to aquatic invertebrates (daphnia)	<i>Daphnia magna</i> Straus	OECD 202, part II (1991)	NOEC = 0.123 mg/L
4.6.2	Toxicity to terrestrial plants	<i>Lolium perenne</i> <i>Brassica rapa</i> <i>Vicia sativa</i>	OECD 208 (1984)	EC <sub>50</sub> > 100 mg/kg
<b>CAS-NO.:</b>		<b>SPECIES</b>	<b>PROTOCOL</b>	<b>RESULTS</b>
<b>TOXICOLOGY</b>				
5.1.1	Acute oral toxicity	Rat	EPA 1978	LD <sub>50</sub> > 5000 mg/kg bw
5.1.2	Acute inhalation toxicity	Rat	Not indicated	LC <sub>50</sub> (4 h) = 55.5 mg/m <sup>3</sup>
5.1.3	Acute dermal toxicity	Rabbit	Not indicated	LD <sub>50</sub> > 3000 mg/kg bw
5.4	Repeated dose toxicity	Rat	Not indicated	LOAEL 70 mg/kg bw
		Rat	Not indicated	LOAEL 220 mg/kg bw
5.5	Genetic toxicity <i>in vitro</i>			
	Bacterial test (gene-mutation)	<i>Salmonella typhimurium</i>	Ames	Negative
	Non-bacterial test (indicator test for gene and/or chromosome mutation)	CHO cells	OECD 473 (1983)	Negative
5.6	Genetic toxicity <i>in vivo</i> (chromosome aberration)		-	-
5.8	Toxicity to reproduction	Rat	OECD 421 (draft update 1994)	NOAEL parental 10 mg/kg bw NOAEL offspring 100 mg/kg bw

5.9	Developmental toxicity / teratogenicity	-	-
5.11	Experience with human exposure	-	-

## SIDS Initial Assessment Report

### 1. Identity and physico-chemical properties

Name	: Metilox
Chemical name	: Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester
Synonyms	: Irganox 1300 TK 10027 Fenozan 1 Hydrocinnamic acid, 3,5-di-tert-butyl-4-hydroxy-, methyl ester Methyl 3,5-di-tert-butyl-4-hydroxyhydrocinnamate Methyl 3-(4-hydroxy-3,5-di-tert-butylphenyl)propionate
Molecular formula	: C <sub>18</sub> H <sub>28</sub> O <sub>3</sub>
Structural formula	:



CAS number	: 6386-38-5
EINECS number	: 228-985-4
Purity	: >99%
Physical state	: Solid (20 °C and 1013 hPa)
Molecular weight	: 292.42
Boiling point	: 335.8 °C
Melting point	: 66.1 °C
Density	: 1.09 g/cm <sup>3</sup> (64 °C)
Vapour pressure	: 0.00002 hPa (25 °C)
Log P <sub>oct/water</sub> *	: 5.5-5.9
Water solubility	: 2.2 mg/L
Autoflammability	: 370 °C
Henry's Law constant	: 0.266 Pa.m <sup>3</sup> /mole (ref 26)

\*The value found for the logKow is a calculated value. This is considered acceptable. Calculations with the Epiwin model gave a logKow of 5.06, which is in good agreement with the reported values.

## 2. Exposure and use

### General information on use

Metilox is the addition product of 2,6-di(tert-butyl)phenol and methylacrylate. It is used as an intermediate in the synthesis of phenolic antioxidants mainly for polymers (ref. 38). This application accounts for 99.8% of the production volume. Other usages known are as an additive in motor oils, hydraulic fluids and as a lubricant.

The use of Metilox in consumer products was reported in Denmark (>10% concentrations in not further specified products) and in Sweden (as a lubricant in motor oils). In Canada Metilox is also used in fragrances/perfumes/deodorisers/flavouring agents (ref. 43).

The total production volume within OECD member states by the major producer (Ciba) amounted 23,500 tonnes in 1992. Known Metilox production sites are in Switzerland and in the U.S.

### Exposure

#### Synthesis of phenolic antioxidants

In Switzerland and in the USA, Metilox is produced by Ciba in a closed system. Waste is recycled or incinerated. During the production and maintenance processes some Metilox is released via wastewater (<0.5 kg/y for the Swiss site, letter from Ciba-Geigy dated 08-09-92). The amount released in water has been reduced after the opening of a new production plant in Switzerland in 1993 (ref. 39). There is no release via air because waste air passes an incinerator. Due to the use of a closed system, worker exposure is considered to be negligible. However, during cleaning operations and if Metilox is packed for use as a direct additive (0.2% of production) exposure may be possible.

Calculations for the  $PEC_{\text{surface water}}$  performed with USES 3.0 (EUSES 1.0 is integral part of this program), are presented in Appendix A. The use of default values considering the production and processing of Metilox can be seen as a worst-case scenario. Based on the total production volume and releases during production and processing a peak PEC of 0.417 mg/L was calculated. The annual PEC was found to be 0.233 mg/L.

If only the release of waste water from a production site is taken into account, a much lower PEC can be calculated. Starting from an annual release of 0.5 kg, a water treatment plant of 2000 m<sup>3</sup> (daily release) and a dilution factor of 10 (default factor used in EUSES 1.0), a PEC surface water can be calculated:

$$PEC = \frac{0.5E06}{2000 * 365 * 10} = 0.068 \text{ mg/m}^3 = 0.000068 \text{ mg/L}$$

Since the Swiss plant is located near the river Rhine, it is expected that the release will be into this river. The flow rate of the Rhine is  $\geq 1260 \text{ m}^3/\text{s}$  (TGD part IV). This means a yearly flow of about  $4E10 \text{ m}^3$ . This will lead to a dilution factor of  $\sim 5500$  ( $4E10 / (2000 * 365)$ ).

Assuming release to the Rhine the following PEC can be calculated:

$$PEC = \frac{0.5E06}{2000 * 365 * 5500} = 1.2E-05 \text{ mg/m}^3 = 1.2E-08 \text{ mg/L}$$

In wastewater of a US plant concentrations of Metilox between 0.6 and 11 mg/L were reported. In the receiving surface water the maximum concentration measured was 0.2 mg/L (ref. 24). These values are in good agreement with the USES 3.0 calculations (Appendix A).

### **Antioxidant in motor oils**

A small quantity of Metilox is used as an antioxidant in engine oils and lubricants. It is estimated that about 35% of all oils and lubricants remain unaccounted (e.g. dumped uncontrolled) during and after use (Ref 44). Because the concentration of Metilox in engine oils and lubricants is about 1 % and only a very small amount of these oils contain Metilox, the exposure of soil and/or water due to dumping of oils is assumed to be small.

Calculations of the  $PEC_{\text{surface water}}$  for this application show very low values (2.1E-03 mg/L, see Appendix A).

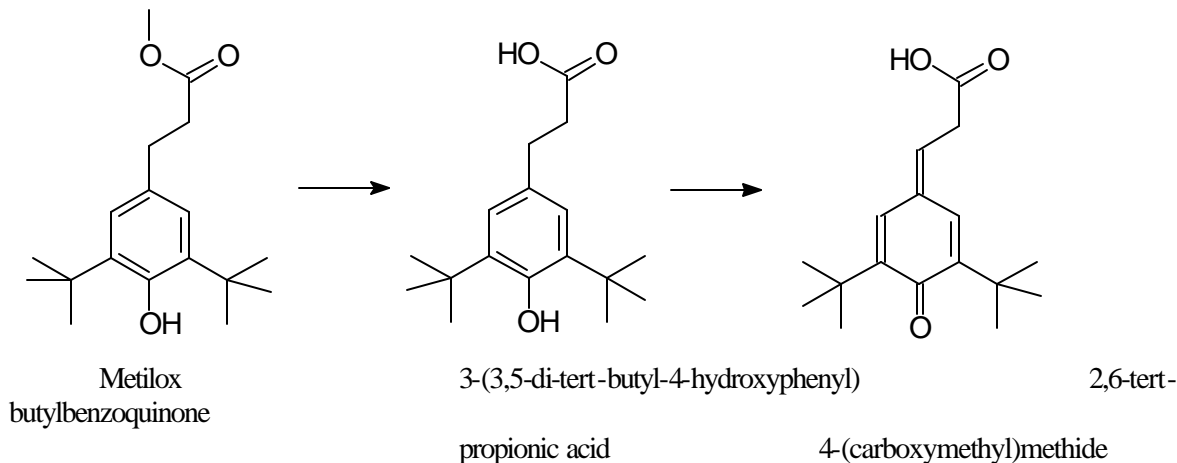
### **Consumer products**

Considering consumer products the reported use of Metilox in some fragrances (expected at concentrations  $\leq 0.1\%$ ) is likely to cause a very small (estimate: 5 mg / person / day) dermal exposure in the people using a particular fragrance. Due to the low vapour pressure inhalatory exposure is not expected. The Dermwin program (Appendix B) and USES 3.0 (Appendix A) predict a very high dermal uptake. Based on the very high log Pow values found for Metilox, it is expected that the calculated values are not reliable and represent an overestimation of the uptake. For substances with similar molecular weight and a comparable log Pow also no dermal penetration is expected.

### 3. Environmental fate

In the presence of a sensitiser (OH radicals) the calculated photolytical half-life of Metilox in air is 19.7 hours (ref 32).

Metilox was found to hydrolyse to the carboxylic acid in natural water and in laboratory model systems containing sediment and high-purity water. This acid is further oxidised towards the quinone (methide) (ref. 25):



In 1975/6 the concentrations of Metilox found in the waste water of an US plant producing antioxidants were between 0.6-11 mg/L (water solubility 2.2 mg/L). Measurements in water and sediment of the receiving river revealed mean concentrations of 0.025 mg/L in surface water and 1.5-170 mg/kg in sediment (ref. 24). For sediment an accumulation factor of 286 was calculated from these results. The hydrolysis product (the acid) was identified, but not quantified in the fractions examined.

The EQC model (ref 42) was used to calculate distribution over the environmental compartments. This model is an extended version of the Mackay-model (level III). According to this model Metilox is distributed in air/soil/water/sediment at 8.5/8.4/2.2/89%, which is in accordance with the monitoring results.

In a CO<sub>2</sub> evolution test over 28 days Metilox was not degraded (ref. 10). In a simulated activated sludge plant of a coupled units test (ref. 36) the potassium salt of 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionic acid was only degraded to a limited extent (21-31%). Therefore it is concluded that both Metilox and the salt of 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionic acid are not readily biodegradable.

#### Conclusion

Although hydrolysis may play a role in the environmental fate of Metilox, it can not be quantified. According to the monitoring data Metilox itself was found in surface water and sediment.

## 4. Ecotoxicity

### Aquatic organisms

The LC<sub>0</sub> and LC<sub>50</sub> found in an acute toxicity study with Zebra fish were above the water solubility of the compound (96-h LC<sub>50</sub> 5.8 mg/L) (ref. 11). The same was seen in a daphnia study with a 24-h EC<sub>50</sub> >100 mg/L (ref. 12). Both tests were performed using a dispersant, which makes the results less realistic (above water solubility). For algae the NOEC for effects on algae growth was 0.5 mg/L (72 h-EC<sub>50</sub> 2.3 mg/L, both based on measured concentrations, no dispersant used, ref. 15).

In a chronic daphnia study a NOEC of 0.123 mg/L (measured concentration) was found (LOEC 0.367 mg/L). At this concentration no effects on mortality/immobility of the parents nor on the total number of young were found (ref. 29).

In carps bioaccumulation of Metilox was established under flow through conditions (432 L/day) for a period of 8 weeks. The substance tested was a mixture containing 6 different esters of metilox acid. For the free acid of metilox the bioaccumulation factor was 60-223 at 50 µg/L and 121-532 at 5 µg/L (ref. 48).

In a respiration inhibition test Metilox was found to inhibit bacterial oxygen consumption only minimal at 33 and 103 mg/L (3-8% (highest doses tested) (ref. 13).

A calculation with the Epiwin model (PCKOC) gave a Koc of 22000 (ref. 47). This value may vary significantly with pH.

### Conclusion

Based on the NOEC found in the daphnia reproduction study and applying a safety factor 50 a PNEC of 2.5 µg/L can be derived.

### Plants

Metilox is not phytotoxic to ryegrass (*Lolium perenne*), turnip (*Brassica rapa*) and vetch (*Vicia sativa*) at concentrations up to 100 mg/kg dw (EC<sub>50</sub> >100 mg/kg)(ref. 14).

## 5 Human health hazards

### Acute toxicity

In acute toxicity tests no major findings of toxicity were reported. In the oral test effects were limited to dyspnoea, ruffled fur, exophthalmos and hunched body posture, while in the dermal test pustules and slight desquamation were observed. All animals survived at the doses tested. The LD<sub>50</sub>/LC<sub>50</sub> values are summarised in table 1.

Table 1: LD<sub>50</sub>/LC<sub>50</sub> values

Species	Route	Value	Reference
Rat	oral	>5000 mg/kg	1
Rat	inhalation	>55.5 mg/m <sup>3</sup>	22
Rat	dermal	>3000 mg/kg	23

The particle size in the inhalation study was >10 µm for more than 95.5% of the particles generated. Therefore it is concluded that exposure to dusts of Metilox will not lead to substantial systemic uptake of the substance via the inhalatory route.

### Irritation and sensitisation

Metilox was not irritating after application to the skin (Draize scoring) or the eyes (ref 2, 3, 41). In a human skin patch test no sensitising properties were found (ref 21).

#### Repeated dose

In a 28-day range finding study 5 rats/sex were fed a diet containing 0, 2000, 10000 and 50000 ppm Metilox. Actual mean intake was calculated to be 0, 220, 660 and 585 mg/kg bw. Food consumption was decreased and water intake increased at 660 and 585 mg/kg bw. The animals at these dose levels were stated to be "in a bad condition". In the high dose group food consumption was minimal and the animals lost about 30% of body weight within the first week. All animals in this group and a female at 660 mg/kg bw died. Liver weight (relative to body weight) was dose dependent increased in all dose groups. Macroscopically this was accompanied by enlargement (at 220 and 660 mg/kg bw) and discoloration (at 660 mg/kg bw). Histological evaluations revealed hepatocytes with homogenous cytoplasm containing eosinophilic droplets and abnormalities of the nucleus (size and chromatin pattern variation, binucleated cells). In females at 660 mg/kg the relative kidney weight was increased. Macroscopically dilation of the tubules was observed (ref. 33).

Rats (10/sex/dose level) were fed Metilox in their diet at levels of 0, 70, 140 and 700 mg/kg during 90 days. In the high dose group 8/10 males and 6/10 females died. Survivors were emaciated, showed re-duced body weights and decreased food and water intake. Leukocyte counts and haemoglobin level were significantly decreased and serum ALP was significantly increased in high dosed animals. In this group organ weights were increased (related to the decreased body weight). Livers were enlarged and discoloured with enlarged hepatocytes with homogenous cytoplasm containing eosinophilic droplets and variation in size and chromatin pattern of the nucleus. Many binucleated cells were observed. Additionally necrosis of parenchymal cells and slight proliferation of the bile ducts was seen. Minimal liver effects consisting of homogenous cytoplasm and nucleus variability (of size) were also seen in animals of the intermediate dose group.

The thyroid was enlarged at the highest dose level. A dose related change of appearance (like in TSH treated rats) of the thyroid became apparent at all dose levels. It was concluded that Metilox

has a goitrogenic effect. Based on this effect it was concluded that the LOAEL derived in this study was 70 mg/kg bw (ref 34).

#### Additional information

The primary effect in the rat is the induction of liver enzymes. This leads to an increase of the elimination rate of thyroid hormones. Feedback-mechanism under control of the pituitary subsequently cause a stimulation of the thyroid. The effect cascade is known to be more pronounced in rats than in higher mammals (ref 45, 46).

### Mutagenicity

#### *In vitro tests*

Metilox was negative in the Ames test with and without metabolic activation (ref 4) and the chromosome aberration test with and without metabolic activation (ref 18). There are no indications for possible mutagenicity of the compound.

#### *In vivo tests*

No data are available on this endpoint.

### Reproduction and developmental toxicity

A range-finding reproduction toxicity screening test was performed. Male and female rats were exposed orally to 0, 50, 250 and 500 mg/kg bw Metilox from 2 weeks pre-mating until 2 weeks post coitum. Reduced body weight (gain) was reported in both males and females mainly during week 1 of the study. Clinical signs included piloerection, hunched posture and reduced activity after administration of the test substance. All females were mated except one at the highest dose level. Necropsy of both males and females was on day 14 post-coitum (i.e. before parturition of the females). At 250 mg/kg 1 female and at 500 mg/kg 2 females appeared non-pregnant. A preliminary conclusion can be that at parental toxic dose levels no effects on reproduction were found (ref. 37).

In a reproduction/developmental toxicity screening test (main test) 15 male and 15 female rats received 0, 10, 100 and 250 mg Metilox/kg bw orally during 2 weeks before mating, during the mating period and 2 weeks thereafter (males) or until day 4 of lactation (females). Body weight and food consumption were decreased in males at 250 mg/kg bw and females at 100 and 250 mg/kg bw. In the parental generation liver effects were seen in both sexes at 100 and 250 mg/kg bw. These effects included increased liver weights (both absolute and relative to body weight) and histopathological changes consisting of hypertrophy of liver cells and an increased cholangiofibrosis of the bile ducts. No effects on mating, fertility and pregnancy rate were seen. All females delivered live pups. At the high dose level litter size, pup weight and pup viability on day 4 were decreased. No gross abnormalities were found in surviving pups. Pups that died were found autolysed (ref. 19).

The NOAEL for parental toxicity is 10 mg/kg bw, based on increased relative liver weight observed in 100 mg/kg bw treatment groups. For developmental effects a NOAEL of 100 mg/kg bw can be derived, based on reduced body weight gain and viability. Developmental effects are only observed at doses that are toxic to the parents.

**Other**

At pH 7.4 Metilox (<sup>14</sup>C-labelled) was rapidly hydrolysed to 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid in rat serum and rat liver homogenate ( $T_{1/2}$  <14 minutes). After oral administration to male rats (9.6 and 8.6 mg/kg bw) the compound was rapidly absorbed (concentration in blood AUC maximum after 2 and 6 hour, second maximum after 10 hours). 94% of Metilox was metabolised to the corresponding carboxylic acid. This metabolite appeared already 15 minutes after treatment in the blood (ref. 16).

After oral administration of 1 and 10 mg/kg bw of <sup>14</sup>C-Metilox to male Wistar rats, 54-58% of the radiolabel was recovered from the faeces after 168 hours. After 48 hours urinary recovery was 32-34% and after 168 the total amount found in urine was 39-42%. At 1 mg/kg bw residue was found in the intestinal tract (0.003 µg/g), blood/plasma (0.006/0.007 µg/g) and carcass (0.002 µg/g). At 10 mg/kg bw most residue was found in the liver (0.1µg/g). Residue levels in the intestinal tract, blood/plasma and carcass were about 10 times higher compared to the levels found after treatment with 1 mg/kg bw.

Maximum plasma concentration after 1 mg/kg bw was reached after 30 minutes ( $T_{1/2}$  6.4 hours). At 10 mg/kg bw a maximum was reached after 30 min and after 8 h ( $T_{1/2}$  7.9 hours) (ref. 30).

**Effects on Humans**

No data are available.

**Existing guidelines**

No data were found.

The producer recommends an exposure limit of 5 mg/m<sup>3</sup> (8 hours TWA, respirable dust in air).

## 6 Conclusion

More than 99.8% of the worldwide production is used as an intermediate in the synthesis of phenolic antioxidants, which go as additives into plastics (major use) and hydraulic fluids or engine oils. It is estimated that < 0.2 % of Metilox is used itself as an antioxidant.

The manufacture of Metilox takes place in a closed process. Worker exposure is therefore expected to be low. Calculations were performed with USES 3.0 to assess environmental PECs.

All physico-chemical endpoints are sufficiently investigated.

Metilox photodegrades in the presence of a sensitiser.

Metilox is not readily biodegradable. The compound hydrolyses to 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid in water. The acid is biodegradable to a limited extent.

From the EQC model it can be deduced that ~89% of Metilox will end up in sediment. This is confirmed by monitoring data taken downstream a contaminated site.

At the water solubility limit Metilox was not acutely toxic towards fish and daphnids. Based on the NOEC found in the daphnia reproduction study (0.123 mg/L) and applying a safety factor 50 a PNEC of 2.5 µg/L was derived.

Metilox was not toxic in acute toxicity tests. The substance is not irritating to the skin and eye. No indications for sensitisation due to Metilox were found.

The data on repeated dose investigations are limited, but reliable. The LOAEL found after oral exposure was 70 mg/kg bw.

Metilox is found to be not mutagenic in the Ames test and in the chromosome aberration test.

No effects on reproductive parameters were found at parental non toxic doses. Effects on the offspring were seen at doses, which produced toxic effects in the parent generation. From the available studies a parental NOAEL of 10 mg/kg bw could be derived.

For developmental effects the NOAEL was 100 mg/kg bw.

## **7 Recommendations**

The substance is currently of low priority for further work.

There is currently no concern for health.

Based on the available data there is currently no concern for the environment. However local, regional or national exposure information gathering may be considered. If that information indicates significant sediment exposure then the hydrolysis rate of Metilox and effects of Metilox and/or degradation products on sediment dwelling organisms should be investigated.

### **Search criteria**

The following data bases were searched under the CAS number 6386-38-5 and Metilox in September 2001: HSDB, Medline, Toxline, Embase, Biosis, Enviroline, Healthstar, Kluwer-Verlagsdatenbank für Volltexte, Springer-Verlagsdatenbank für Volltexte and ZEBET. No additional references were identified.

**8. References**

1. Ciba (1981). Acute Oral LD50 in the Rat of TK 10027. Unpublished report # 811496. December 18, 1981.
2. Ciba (1982a). Skin Irritation in the Rabbit After Single Application of TK 10027. Unpublished report # 811498. March 17, 1982.
3. Ciba (1982b). Eye Irritation in the Rabbit After Single Application of TK 10027. Unpublished report # 811497. March 17, 1982.
4. Ciba (1983). Salmonella/Mammalian-Microsome Mutagenicity Test. Test Material: TK 10027 (Metilox). Unpublished report # 830491. August 3, 1983.
5. Ciba (1987). Internal report. Additives Division. July 3, 1987.
6. Ciba (1989a). Internal report. Analytical Chemistry. September 21, 1989.
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Appendix A  
USES 3.0

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
<b>SUBSTANCE</b>				
<b>SUBSTANCE IDENTIFICATION</b>				
General name	Metilox	Metilox		S
Description	Use	Use		S
CAS-No	6386-38-5	6386-38-5		S
EC-notification no.	n.a.	n.a.		S
EINECS no.	n.a.	n.a.		S
<b>PHYSICO-CHEMICAL PROPERTIES</b>				
Molecular weight	292.42	292.42	[g.mol <sup>-1</sup> ]	S
Melting point	66.1	66.1	[°C]	S
Boiling point	335.8	335.8	[°C]	S
Vapour pressure at 25 [°C]	2E-03	2E-03	[Pa]	S
Octanol-water partition coefficient	5.91	5.91	[log10]	S
Water solubility	2.2	2.2	[mg.l <sup>-1</sup> ]	S

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
RELEASE ESTIMATION				
CHARACTERIZATION AND TONNAGE				
High Production Volume Chemical	Yes	Yes		S
Production volume of chemical in EU	2.35E+04	2.35E+04	[tonnes.yr-1]	S
Volume of chemical imported to EU	0	0	[tonnes.yr-1]	D
Volume of chemical exported from EU	0	0	[tonnes.yr-1]	D
Intermittent release	No	No		D
USE PATTERNS				
EMISSION INPUT DATA[USE PATTERN 1]				
Industry category	5 Personal / domestic use	5 Personal / domestic use		S
Use category	55/0 Others	55/0 Others		S
Emission scenario document available	Yes	Yes		O
Extra details on use category	No extra details necessary	No extra details necessary		D
Extra details on use category	No extra details necessary	No extra details necessary		D
Fraction of tonnage for application	7E-04	7E-04	[-]	O
Fraction of chemical in formulation	0.1	0.1	[-]	S
Production	No	No		S
Formulation	No	No		S
Processing	No	No		S
Private use	Yes	Yes		D
Recovery	No	No		S
Main category production	III Multi-purpose equipment	III Multi-purpose equipment		D
Main category formulation	III Multi-purpose equipment	III Multi-purpose equipment		D
Main category processing	III Non-dispersive use	III Non-dispersive use		D
EMISSION INPUT DATA[USE PATTERN 2]				
Industry category	9 Mineral oil and fuel industry	9 Mineral oil and fuel industry		S
Use category	35 Lubricants and additives	35 Lubricants and additives		S
Emission scenario document available	No	No		O
Extra details on use category	No extra details necessary	No extra details necessary		D
Extra details on use category	No extra details necessary	No extra details necessary		D
Fraction of tonnage for application	1.3E-03	1.3E-03	[-]	S
Fraction of chemical in formulation	0.1	0.1	[-]	S
Production	No	No		S
Formulation	Yes	Yes		D
Processing	Yes	Yes		S
USES 3.0	9/6/01 3:06:39 PM			Page: 3

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
EMISSION INPUT DATA[USE PATTERN 2] ( Continued )				
Private use	Yes	Yes		S
Recovery	No	No		S
Main category production	Ic Intermed. stored off-site/dedicated equip.	Ic Intermed. stored off-site/dedicated equip.		S
Main category formulation	III Multi-purpose equipment	III Multi-purpose equipment		D
Main category processing	IV Wide dispersive use	IV Wide dispersive use		S
EMISSION INPUT DATA[USE PATTERN 3]				
Industry category	3 Chemical industry: chemicals used in synthesis	3 Chemical industry: chemicals used in synthesis		S
Use category	33 Intermediates	33 Intermediates		S
Emission scenario document available	Yes	Yes		O
Extra details on use category	Substance processed elsewhere	Substance processed elsewhere		S
Extra details on use category	No extra details necessary	No extra details necessary		D
Fraction of tonnage for application	0.998	0.998	[-]	S
Fraction of chemical in formulation	1	1	[-]	D
Production	Yes	Yes		S
Formulation	No	No		S
Processing	Yes	Yes		S
Private use	No	No		S
Recovery	No	No		S
Main category production	Ic Intermed. stored off-site/dedicated equip.	Ic Intermed. stored off-site/dedicated equip.		S
Main category formulation	III Multi-purpose equipment	III Multi-purpose equipment		D
Main category processing	Ic Dedicated equipment	Ic Dedicated equipment		S
LOCAL				
[USE PATTERN 3] [PRODUCTION]				
Show this step in further calculations	Yes	No		S
[USE PATTERN 3] [PROCESSING]				
Show this step in further calculations	Yes	No		S
USES 3.0				
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Page: 4				

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
DISTRIBUTION				
CONTINENTAL AND REGIONAL				
CONTINENTAL				
Continental PEC in surface water (total)	7.48E-05	7.48E-05	[mg.l-1]	O
Continental PEC in sea water (total)	??	??	[mg.l-1]	D
Continental PEC in surface water (dissolved)	6.16E-05	6.16E-05	[mg.l-1]	O
Continental PEC in sea water (dissolved)	??	??	[mg.l-1]	D
Continental PEC in air (total)	1.85E-07	1.85E-07	[mg.m-3]	O
Continental PEC in agricultural soil (total)	0.317	0.317	[mg.kgwwt-1]	O
Continental PEC in pore water of agricultural soils	2.33E-04	2.33E-04	[mg.l-1]	O
Continental PEC in natural soil (total)	4.58E-03	4.58E-03	[mg.kgwwt-1]	O
Continental PEC in industrial soil (total)	0.0621	0.0621	[mg.kgwwt-1]	O
Continental PEC in sediment (total)	0.182	0.182	[mg.kgwwt-1]	O
Continental PEC in sea water sediment (total)	??	??	[mg.kgwwt-1]	D
REGIONAL				
Regional PEC in surface water (total)	3.55E-04	3.55E-04	[mg.l-1]	O
Regional PEC in sea water (total)	??	??	[mg.l-1]	D
Regional PEC in surface water (dissolved)	3.12E-04	3.12E-04	[mg.l-1]	O
Regional PEC in sea water (dissolved)	??	??	[mg.l-1]	D
Regional PEC in air (total)	3.12E-07	3.12E-07	[mg.m-3]	O
Regional PEC in agricultural soil (total)	3.07	3.07	[mg.kgwwt-1]	O
Regional PEC in pore water of agricultural soils	2.26E-03	2.26E-03	[mg.l-1]	O
Regional PEC in natural soil (total)	7.7E-03	7.7E-03	[mg.kgwwt-1]	O
Regional PEC in industrial soil (total)	0.57	0.57	[mg.kgwwt-1]	O
Regional PEC in sediment (total)	0.919	0.919	[mg.kgwwt-1]	O
Regional PEC in sea water sediment (total)	??	??	[mg.kgwwt-1]	D
LOCAL PECS [PRIVATE USE]				
Annual average local PEC in air (total)	3.12E-07	3.12E-07	[mg.m-3]	O
Local PEC in surface water during emission episode	3.18E-04	3.18E-04	[mg.l-1]	O
Annual average local PEC in surface water (dissolved)	3.18E-04	3.18E-04	[mg.l-1]	O
Local PEC in sediment during emission episode	0.534	0.534	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 30 days	0.0218	0.0218	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 180 days	0.0218	0.0218	[mg.kgwwt-1]	O
Local PEC in grassland (total) averaged over 180 days	0.0133	0.0133	[mg.kgwwt-1]	O
Local PEC in pore water of agricultural soil	1.6E-05	1.6E-05	[mg.l-1]	O
Local PEC in pore water of grassland	9.78E-06	9.78E-06	[mg.l-1]	O
Local PEC in groundwater under agricultural soil	0.016	0.016	[ug.l-1]	O
LOCAL PECS [FORMULATION]				
Annual average local PEC in air (total)	6.13E-06	6.13E-06	[mg.m-3]	O
Local PEC in surface water during emission episode	1.76E-03	1.76E-03	[mg.l-1]	O
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USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
LOCAL PECS [FORMULATION] ( Continued )				
Annual average local PEC in surface water (dissolved)	1.5E-03	1.5E-03	[mg.l-1]	O
Local PEC in sediment during emission episode	2.96	2.96	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 30 days	3.18	3.18	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 180 days	3.18	3.18	[mg.kgwwt-1]	O
Local PEC in grassland (total) averaged over 180 days	1.28	1.28	[mg.kgwwt-1]	O
Local PEC in pore water of agricultural soil	2.34E-03	2.34E-03	[mg.l-1]	O
Local PEC in pore water of grassland	9.37E-04	9.37E-04	[mg.l-1]	O
Local PEC in groundwater under agricultural soil	2.34	2.34	[ug.l-1]	O
LOCAL PECS [PROCESSING]				
Annual average local PEC in air (total)	4.26E-07	4.26E-07	[mg.m-3]	O
Local PEC in surface water during emission episode	3.27E-04	3.27E-04	[mg.l-1]	O
Annual average local PEC in surface water (dissolved)	3.27E-04	3.27E-04	[mg.l-1]	O
Local PEC in sediment during emission episode	0.549	0.549	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 30 days	0.041	0.041	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 180 days	0.041	0.041	[mg.kgwwt-1]	O
Local PEC in grassland (total) averaged over 180 days	0.021	0.021	[mg.kgwwt-1]	O
Local PEC in pore water of agricultural soil	3.01E-05	3.01E-05	[mg.l-1]	O
Local PEC in pore water of grassland	1.54E-05	1.54E-05	[mg.l-1]	O
Local PEC in groundwater under agricultural soil	0.0301	0.0301	[ug.l-1]	O
LOCAL PECS [PRIVATE USE]				
Annual average local PEC in air (total)	3.12E-07	3.12E-07	[mg.m-3]	O
Local PEC in surface water during emission episode	3.12E-04	3.12E-04	[mg.l-1]	O
Annual average local PEC in surface water (dissolved)	3.12E-04	3.12E-04	[mg.l-1]	O
Local PEC in sediment during emission episode	0.524	0.524	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 30 days	7.83E-03	7.83E-03	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 180 days	7.83E-03	7.83E-03	[mg.kgwwt-1]	O
Local PEC in grassland (total) averaged over 180 days	7.75E-03	7.75E-03	[mg.kgwwt-1]	O
Local PEC in pore water of agricultural soil	5.75E-06	5.75E-06	[mg.l-1]	O
Local PEC in pore water of grassland	5.69E-06	5.69E-06	[mg.l-1]	O
Local PEC in groundwater under agricultural soil	5.75E-03	5.75E-03	[ug.l-1]	O
USES 3.0	9/6/01 3:06:39 PM	Page: 6		

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
EXPOSURE				
CONSUMER EXPOSURE				
INPUT				
INHALATION				
Time scale of inhalatory exposure	(Sub-)Chronic	(Sub-)Chronic		D
Number of events	??	??	[d-1]	D
Duration of contact per event	??	??	[hr]	D
Amount of product released	??	??	[mg]	D
Weight fraction of substance in product	??	??	[-]	D
Room volume	??	??	[m3]	D
DERMAL				
Scenario for dermal exposure	A : Substance contained in a medium	A : Substance contained in a medium		D
Time scale of dermal exposure	(Sub-)Chronic	(Sub-)Chronic		D
Number of events	??	??	[d-1]	D
Exposed body part	Total	Total		D
Surface area of exposed skin	1.94	1.94	[m2]	O
Average concentration of substance in product	??	??	[mg.cm-3]	O
Concentration of substance in undiluted product	??	??	[mg.cm-3]	O
Density of product before dilution	??	??	[mg.cm-3]	O
Amount of undiluted product used	??	??	[mg]	D
Volume of product before dilution	??	??	[cm3]	D
Weight fraction of substance in product	??	??	[-]	D
Dilution factor	??	??	[-]	D
Volume of diluted product contacting the skin	194	194	[cm3]	O
Thickness of layer of product on skin	0.01	0.01	[cm]	D
Weight of substance on skin per event	??	??	[mg.cm-2]	D
Fraction of substance migrating per unit time	??	??	[hr-1]	D
Duration of contact per event	??	??	[hr]	D
ORAL				
Scenario for oral exposure	A : Substance in a product swallowed	A : Substance in a product swallowed		D
Time scale of oral exposure	(Sub-)Chronic	(Sub-)Chronic		D
Number of events	??	??	[d-1]	D
Volume of diluted product in contact with mouth	??	??	[cm3]	D
Concentration of substance in undiluted product	??	??	[mg.cm-3]	O
Density of product before dilution	??	??	[mg.cm-3]	O
Amount of undiluted product used	??	??	[mg]	D
Volume of product before dilution	??	??	[cm3]	D
Weight fraction of substance in product	??	??	[-]	D
Dilution factor	??	??	[-]	D
Fraction of product swallowed	??	??	[-]	D
Surface area of article in contact with food	??	??	[cm2]	D
Thickness of article in contact with food	??	??	[cm]	D
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USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
ORAL ( Continued )				
Concentration of substance in article	??	??	[mg.cm-3]	D
Fraction of substance migrating per unit time	??	??	[hr-1]	D
Volume of food	??	??	[cm3]	D
Duration of contact per event	??	??	[hr]	D
INTERMEDIATE RESULTS				
INHALATION				
Concentration in air of room	??	??	[mg.m-3]	O
Inhalatory intake	??	??	[mg.kgbw-1.d-1]	O
DERMAL				
Scenario for dermal exposure	A : Substance contained in a medium	A : Substance contained in a medium		D
Average concentration of substance in product	??	??	[mg.cm-3]	O
Weight of substance on skin per event	??	??	[mg.cm-2]	D
Amount of substance on skin	??	??	[mg]	O
Amount of substance on skin due to migration	??	??	[mg.kgbw-1.d-1]	D
Potential dermal uptake	??	??	[mg.kgbw-1.d-1]	O
ORAL				
Scenario for oral exposure	A : Substance in a product swallowed	A : Substance in a product swallowed		D
Concentration in product swallowed	??	??	[mg.cm-3]	O
Ingestion rate of substance	??	??	[mg.kgbw-1.d-1]	O
CHRONIC EXPOSURE				
Annual average inhalation exposure concentration	??	??	[mg.m-3]	O
Annual average dermal exposure concentration	??	??	[mg.cm-3]	O
Annual average oral exposure concentration	??	??	[mg.cm-3]	O
TOTAL EXPOSURE				
Total chronic uptake via different routes	0	0	[mg.kgbw-1.d-1]	O
Total acute uptake via different routes	0	0	[mg.kgbw-1.d-1]	O
HUMAN EXPOSURE AT THE WORKPLACE				
SUBSTANCE DATA AND PATTERN OF USE				
SUBSTANCE PROPERTIES				
Physical state of a substance	Solid	Solid		O
Process temperature	20	20	[oC]	S
Determination of Vapour Pressure	Measured at process temperature	Measured at process temperature		D
Vapour pressure at the process temperature	1.23E-03	1.23E-03	[Pa]	O
Aerosol formed	No	No		D
Inhalation exposure to dust particles	No	No		O
Particle size of the substance	Granular	Granular		D
USES 3.0	9/6/01 3:06:39 PM			Page: 8

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
HUMAN EXPOSURE AT THE WORKPLACE ( Continued )				
SUBSTANCE DATA AND PATTERN OF USE				
SUBSTANCE PROPERTIES				
Type of dust	Non-Fibrous	Non-Fibrous		D
Ability of fibrous dust to become airborne	High	High		D
Dust particles aggregates readily	No	No		D
PATTERN OF USE				
Pattern of use	Wide dispersive use	Wide dispersive use		S
Is closed system (considered to be) breached	No	No		D
Pattern of control applied to the process	Direct handling	Direct handling		S
Type of process operations	Dry crushing & grinding	Dry crushing & grinding		D
Local Exhaust Ventilation (LEV) present	No	No		D
DERMAL DATA				
Amount of dermal contact between worker and substance	Intermittent	Intermittent		S
Area of contact between substance and skin	0.084	0.084	[m2]	O
Thickness of layer of product on skin	0.01	0.01	[cm]	D
Mean number of events	4	4	[d-1]	S
Pattern of control applied to the process	Direct handling	Direct handling		O
INTERMEDIATE RESULTS				
INHALATION				
Vapour concentration in air for workers	0 - 0.1	0 - 0.1	[ppm]	O
Vapour concentration in air for workers	0 - 1.22	0 - 1.22	[mg.m-3]	O
Fibre concentration in air for workers	0 - 0	0 - 0	[fibres.m-3]	O
Dust concentration in air for workers	0 - 0	0 - 0	[mg.m-3]	O
DERMAL				
Dermal weight of substance on the skin of workers	1 - 5	1 - 5	[mg.cm-2.d-1]	O
Potential dermal uptake for workers	0.012 - 0.06	0.012 - 0.06	[g.kgbw-1.d-1]	O

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
EFFECTS				
INPUT OF EFFECTS DATA				
MICRO-ORGANISMS				
EC50 for micro-organisms in a STP	>100	>100	[mg.l-1]	S
Specific bacterial population?	No	No		D
EC10 for micro-organisms in a STP	??	??	[mg.l-1]	D
Specific bacterial population?	No	No		D
NOEC for micro-organisms in a STP	??	??	[mg.l-1]	D
Specific bacterial population?	No	No		D
AQUATIC ORGANISMS				
LC50 for fish	>2.2	>2.2	[mg.l-1]	S
L(E)C50 for Daphnia	>2.2	>2.2	[mg.l-1]	S
EC50 for algae	2.3	2.3	[mg.l-1]	S
LC50 for other aquatic species	??	??	[mg.l-1]	D
Species	other	other		D
NOEC for fish	??	??	[mg.l-1]	D
NOEC for Daphnia	0.123	0.123	[mg.l-1]	S
NOEC for algae	0.5	0.5	[mg.l-1]	S
NOEC for other aquatic species	??	??	[mg.l-1]	D
Additional aquatic NOEC	??	??	[mg.l-1]	D
Additional aquatic NOEC	??	??	[mg.l-1]	D
Additional aquatic NOEC	??	??	[mg.l-1]	D
Additional aquatic NOEC	??	??	[mg.l-1]	D
Additional aquatic NOEC	??	??	[mg.l-1]	D
TERRESTRIAL ORGANISMS				
LC50 for plants	>100	>100	[mg.kgdwt-1]	S
LC50 for earthworms	??	??	[mg.kgdwt-1]	D
EC50 for microorganisms	??	??	[mg.kgdwt-1]	D
LC50 for other terrestrial species	??	??	[mg.kgdwt-1]	D
Species	other	other		D
NOEC for plants	??	??	[mg.kgdwt-1]	D
NOEC for earthworms	??	??	[mg.kgdwt-1]	D
NOEC for microorganisms	??	??	[mg.kgdwt-1]	D
NOEC for other terrestrial species	??	??	[mg.kgdwt-1]	D
Additional terrestrial NOEC	??	??	[mg.kgdwt-1]	D
Additional terrestrial NOEC	??	??	[mg.kgdwt-1]	D
Additional terrestrial NOEC	??	??	[mg.kgdwt-1]	D
Additional terrestrial NOEC	??	??	[mg.kgdwt-1]	D
Additional terrestrial NOEC	??	??	[mg.kgdwt-1]	D
Additional terrestrial NOEC	??	??	[mg.kgdwt-1]	D
BIRDS				
LC50 in avian dietary study (5 days)	??	??	[mg.kgfd-1]	D
LD50 for birds	??	??	[mg.kgbw-1]	D
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USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
<b>BIRDS ( Continued )</b>				
NOAEL for birds	??	??	[mg.kgbw-1.d-1]	D
NOEC via food	??	??	[mg.kgfd-1]	O
Duration of (sub-)chronic oral test	Chronic	Chronic		D
Conversion factor NOAEL to NOEC	8	8	[kg.d.kg-1]	D
<b>MAMMALS</b>				
<b>ACUTE</b>				
Oral LD50	>5E+03	>5E+03	[mg.kgbw-1]	S
Oral Discriminatory Dose	??	??	[mg.kg-1]	D
Dermal LD50	>3E+03	>3E+03	[mg.kgbw-1]	S
Inhalatory LC50	>55.5	>55.5	[mg.m-3]	S
<b>(SUB)CHRONIC</b>				
Oral NOAEL	10	10	[mg.kgbw-1.d-1]	S
Oral LOAEL	70	70	[mg.kgbw-1.d-1]	S
Inhalatory NOAEL	46.7	46.7	[mg.m-3]	O
Inhalatory LOAEL	327	327	[mg.m-3]	O
Dermal NOAEL	10	10	[mg.kgbw-1.d-1]	O
Dermal LOAEL	70	70	[mg.kgbw-1.d-1]	O
Inhalatory (fibre) NOAEL	??	??	[fibres.m-3]	D
Inhalatory (fibre) LOAEL	??	??	[fibres.m-3]	D
<b>FOOD</b>				
NOEC via food	100	100	[mg.kg-1]	O
LOEC via food	??	??	[mg.kg-1]	D
Duration of (sub-)chronic oral test	28 days	28 days		D
Species for conversion of NOAEL to NOEC	Rattus norvegicus (<6 weeks)	Rattus norvegicus (<6 weeks)		D
Conversion factor NOAEL to NOEC	10	10	[kg.d.kg-1]	O
Test duration for mammalian toxicity test	28	28	[d]	D
Mammalian species of concern	Dutch standard mammal	Dutch standard mammal		D
Mean bodyweight of mammalian species of concern	??	??	[g]	D
Daily food intake for mammalian species of concern	??	??	[gdwt.d-1]	D
Daily water intake of mammalian species of choice	??	??	[ml.d-1]	D
<b>HUMANS</b>				
<b>ACUTE</b>				
Oral NOAEL	??	??	[mg.kg-1]	D
Oral LOAEL	??	??	[mg.kg-1]	D
Inhalatory NOAEL	??	??	[mg.m-3]	O
Inhalatory LOAEL	??	??	[mg.m-3]	O
Dermal NOAEL	??	??	[mg.kg-1]	O
Dermal LOAEL	??	??	[mg.kg-1]	O
Dermal NOEC in a medium	??	??	[mg.cm-3]	D
Dermal LOEC in a medium	??	??	[mg.cm-3]	D
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USES Compact report		Single substance		
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Study Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
<b>(SUB)CHRONIC</b>				
Oral NOAEL	??	??	[mg.kgbw-1.d-1]	D
Oral LOAEL	??	??	[mg.kgbw-1.d-1]	D
Dermal NOEC in a medium	??	??	[mg.cm-3]	D
Dermal LOEC in a medium	??	??	[mg.cm-3]	D
Dermal LOAEL	??	??	[mg.kgbw-1.d-1]	O
Dermal NOAEL	??	??	[mg.kgbw-1.d-1]	O
Inhalatory LOAEL	??	??	[mg.m-3]	O
Inhalatory NOAEL	??	??	[mg.m-3]	O
Inhalatory (fibre) NOAEL	??	??	[fibres.m-3]	D
Inhalatory (fibre) LOAEL	??	??	[fibres.m-3]	D
<b>CURRENT CLASSIFICATION</b>				
Corrosive (C, R34 or R35)	No	No		D
Irritating to skin (Xi, R38)	No	No		D
Irritating to eyes (Xi, R36)	No	No		D
Risk of serious damage to eyes (Xi, R41)	No	No		D
Irritating to respiratory system (Xi, R37)	No	No		D
May cause sensitisation by inhalation (Xn, R42)	No	No		D
May cause sensitisation by skin contact (Xi, R43)	No	No		D
May cause cancer (T, R45)	No	No		D
May cause cancer by inhalation (T, R49)	No	No		D
Possible risk of irreversible effects (Xn, R40)	No	No		D
<b>ENVIRONMENTAL EFFECTS ASSESSMENT</b>				
<b>INTERMEDIATE RESULTS AQUATIC ORGANISMS, MICRO-ORGANISMS AND PREDATORS</b>				
Toxicological data used for extrapolation to PNEC Aqua	0.123	0.123	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC Aqua	50	50	[-]	O
Toxicological data used for extrapolation to PNEC Aqua	>2.2	>2.2	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC Aqua	100	100	[-]	O
Toxicological data used for extrapolation to PNEC micro	>100	>100	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC micro	100	100	[-]	O
Toxicological data used for extrapolation to PNEC oral	100	100	[mg.kg-1]	O
Assessment factor applied in extrapolation to PNEC oral	100	100	[-]	O
<b>INTERMEDIATE RESULTS TERRESTRIAL AND SEDIMENT ORGANISMS</b>				
Toxicological data used for extrapolation to PNEC Terr	>100	>100	[mg.kgdwt-1]	O
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USES Compact report		Single substance		
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Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
INTERMEDIATE RESULTS TERRESTRIAL AND SEDIMENT ORGANISMS ( Continued )				
Assessment factor applied in extrapolation to PNEC	1000	1000	[-]	O
Terr				
Equilibrium partitioning used for PNEC in soil?	No	No		O
Equilibrium partitioning used for PNEC in sediment?	Yes	Yes		O
PNECS FOR AQUATIC ORGANISMS, MICRO-ORGANISMS AND PREDATORS				
PNEC for aquatic organisms	2.46E-03	2.46E-03	[mg.l-1]	O
PNEC for aquatic organisms, intermittent releases	>0.022	>0.022	[mg.l-1]	O
PNEC for micro-organisms in a STP	>1	>1	[mg.l-1]	O
PNEC for secondary poisoning of birds and mammals	1	1	[mg.kg-1]	O
PNEC for aquatic organisms with statistical method	??	??	[mg.l-1]	O
PNECS FOR TERRESTRIAL AND SEDIMENT ORGANISMS				
PNEC for terrestrial organisms	>0.1	>0.1	[mg.kgdwt-1]	O
PNEC for terrestrial organisms with statistical method	??	??	[mg.kgdwt-1]	O
PNEC for sediment-dwelling organisms	9.5	9.5	[mg.kgdwt-1]	O

USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
RISK CHARACTERIZATION				
ENVIRONMENTAL EXPOSURE				
LOCAL				
RISK CHARACTERIZATION OF [USE PATTERN 1] [PRIVATE USE]				
ENVIRONMENTAL				
RCR for the local water compartment	0.129	0.129	[-]	O
Intermittent release	No	No		D
RCR for the local soil compartment	<0.247	<0.247	[-]	O
Extra factor 10 applied to PEC	No	No		O
RCR for the local sediment compartment	1.46	1.46	[-]	O
Extra factor 10 applied to PEC	Yes	Yes		O
RCR for the sewage treatment plant	<7.16E-05	<7.16E-05	[-]	O
PREDATORS				
RCR for fish-eating birds and mammals	6.64	6.64	[-]	O
RCR for worm-eating birds and mammals	36.9	36.9	[-]	O
HUMANS				
MOS local, total exposure via all media	862	862	[-]	O
MOS local, exposure via air	1.5E+08	1.5E+08	[-]	O
RISK CHARACTERIZATION OF [USE PATTERN 2] [FORMULATION]				
ENVIRONMENTAL				
RCR for the local water compartment	0.717	0.717	[-]	O
Intermittent release	No	No		D
RCR for the local soil compartment	<36.1	<36.1	[-]	O
Extra factor 10 applied to PEC	No	No		O
RCR for the local sediment compartment	8.1	8.1	[-]	O
Extra factor 10 applied to PEC	Yes	Yes		O
RCR for the sewage treatment plant	<0.0162	<0.0162	[-]	O
PREDATORS				
RCR for fish-eating birds and mammals	19.1	19.1	[-]	O
RCR for worm-eating birds and mammals	74.7	74.7	[-]	O
HUMANS				
MOS local, total exposure via all media	77.6	77.6	[-]	O
MOS local, exposure via air	7.61E+06	7.61E+06	[-]	O
RISK CHARACTERIZATION OF [USE PATTERN 2] [PROCESSING]				
ENVIRONMENTAL				
RCR for the local water compartment	0.133	0.133	[-]	O
Intermittent release	No	No		D
RCR for the local soil compartment	<0.464	<0.464	[-]	O
Extra factor 10 applied to PEC	No	No		O
RCR for the local sediment compartment	1.5	1.5	[-]	O
Extra factor 10 applied to PEC	Yes	Yes		O
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USES Compact report		Single substance		
Printed on	9/6/01 3:06:39 PM			
Study	Metilox			
Substance	Metilox			
Defaults	Standard			
Assessment types	1A, 1B, 2, 3A, 3B, 4, 5			
Base set complete	No			
Name	Reference	Value	Units	Status
RISK CHARACTERIZATION OF [USE PATTERN 2] [PROCESSING] ( Continued )				
ENVIRONMENTAL				
RCR for the sewage treatment plant	<1.7E-04	<1.7E-04	[-]	O
PREDATORS				
RCR for fish-eating birds and mammals	6.72	6.72	[-]	O
RCR for worm-eating birds and mammals	37.2	37.2	[-]	O
HUMANS				
MOS local, total exposure via all media	809	809	[-]	O
MOS local, exposure via air	1.1E+08	1.1E+08	[-]	O
RISK CHARACTERIZATION OF [USE PATTERN 2] [PRIVATE USE]				
ENVIRONMENTAL				
RCR for the local water compartment	0.127	0.127	[-]	O
Intermittent release	No	No		D
RCR for the local soil compartment	<0.0888	<0.0888	[-]	O
Extra factor 10 applied to PEC	No	No		O
RCR for the local sediment compartment	1.43	1.43	[-]	O
Extra factor 10 applied to PEC	Yes	Yes		O
RCR for the sewage treatment plant	<6.5E-07	<6.5E-07	[-]	O
PREDATORS				
RCR for fish-eating birds and mammals	6.57	6.57	[-]	O
RCR for worm-eating birds and mammals	36.8	36.8	[-]	O
HUMANS				
MOS local, total exposure via all media	905	905	[-]	O
MOS local, exposure via air	1.5E+08	1.5E+08	[-]	O
REGIONAL				
ENVIRONMENT				
RCR for the regional water compartment	0.127	0.127	[-]	O
RCR for the regional soil compartment	<34.8	<34.8	[-]	O
Extra factor 10 applied to PEC	No	No		O
RCR for the regional sediment compartment	2.52	2.52	[-]	O
Extra factor 10 applied to PEC	Yes	Yes		O
HUMANS				
MOS regional, total exposure via all media	119	119	[-]	O
MOS regional, exposure via air	1.5E+08	1.5E+08	[-]	O
CONSUMER EXPOSURE				
INHALATION				
MOS acute, inhalatory	??	??	[-]	O
MOS chronic, inhalatory	??	??	[-]	O
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## Appendix B

Dermwin

Kp (est): 0.123 cm/hr

SMILES : O=C(OC)CCc(cc(c(O)c1C(C)(C)C(C)(C)C)c1

CHEM : Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl  
ester

MOL FOR: C18 H28 O3

MOL WT : 292.42

----- Dermwin v1.42 -----

Log Kow (estimated) : 5.06

Log Kow (experimental): not available

GENERAL Equation:  $\log Kp = -2.72 + 0.71 \log Kow - 0.0061 MW$ 

Kp (predicted): 1.23e-001 cm/hr

PHENOL Class Equation:  $\log Kp = -0.36(\log Kow)^2 + 2.39(\log Kow) - 5.2$ 

Kp (predicted): 4.73e-003 cm/hr

Dermally Absorbed Dose per Event:

Water Conc (mg/cm3): 8e+002 (entered by user)

Event Duration (hr): 0.25

DA(event): 25 mg/cm2-event (using Fick's first law)

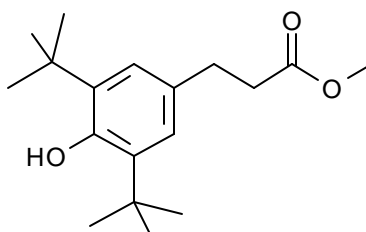
DA(event): 3.1e+002 mg/cm2-event (using eqn 5.20 &amp; 5.21)

(tau = 5.3 hr, t\* = 26 hr)

***SIDS DOSSIER***  
***METILOX***  
***CAS No. 6386-38-5***

**1. General Information****1.01 SUBSTANCE INFORMATION**

- A. CAS-number** 6386-38-5
- B. Name (CAS name)** Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester
- C. Name (OECD name)** Metilox
- E. EINECS-Number** 228-985-4
- F. Molecular Formula** C<sub>18</sub>H<sub>28</sub>O<sub>3</sub>
- G. Structural Formula**



Smiles code:

Oc1c(cc(cc1C(C)(C)C)CCC(=O)OC)C(C)(C)C

- J. Molecular Weight** 292.42

**1.02 OECD INFORMATION**

- A. Sponsor Country:** Switzerland
- B. Lead Organisation** Swiss Agency for the Environment, Forests and Landscape
- Contact Person: Dr. Georg Karlaganis  
Swiss Agency for the Environment, Forests and Landscape  
CH - 3003 Berne, Switzerland  
Tel. +41 31 322 69 55  
Fax +41 31 324 79 78
- C. Name of Responder:** Ciba Specialty Chemicals Ltd.
- Contact Person: Dr. Peter Dollenmeier  
Ciba Specialty Chemicals Ltd.  
P.O. Box WRO-1045.1.35  
CH-4002 Basel, Switzerland  
Tel. +41 61 6366758  
Fax +41 61 6368601

**1.1 GENERAL  
SUBSTANCE  
INFORMATION**

**A. Type of Substance** organic

**B. Physical State** (at 20°C  
and 1013 hPa) solid

**C. Purity** > 99 %

**1.2 SYNONYMS**

TK 10027

Fenozan 1

Hydrocinnamic acid, 3,5-di-tert-butyl-4-hydroxy-, methyl ester

Methyl 3,5-di-tert-butyl-4-hydroxyhydrocinnamate

Methyl 3-(4-hydroxy-3,5-di-tert-butylphenyl)propionate

Irganox 1300

**1.3 IMPURITIES**

CAS No: 128-39-2

EINECS No: 2048840

Name: Phenol, 2,6-di-tert-butyl-

Value: <0.5%

**1.4 ADDITIVES**

No additives

**1.5 QUANTITY**

Ciba is the major producer of Metilox within the OECD member countries. There are other producers within and outside the OECD member states.

Ciba's production levels within OECD:

1992: 23'500 tonnes

**1.6 LABELLING AND  
CLASSIFICATION**

Production volumes of other companies are not known

Label

Type: European Directive 67/548/EC

N;

Dangerous for the environment

**Classification**

R51 / 53:

Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S61

Avoid release to the environment Refer to special instructions/Safety data sheets

**Type: Transport Classification**

ADR/RID Class: 9, Cipher: 12C, UN-No: 3077

IMO Class: Free

ICAO Class: Free

**1.7 Use Pattern**

**A. General**

Type of Use:

Category:

(a) type

Non dispersive use

	industrial use	Chemical industry: chemicals used in synthesis e.g. intermediates Intermediates
(b)	type industrial use	Wide dispersive use Personal and domestic use Lubricants and additives

## Remarks:

- a) Use as intermediate in the synthesis of phenolic antioxidants mainly for polymers (~ 99.8% of the production volume).
- b) Use as a component in additives for motor oils and lubricants (~ 0.2% of the production volume).

Reference: (a), (b) Ciba

## B. Uses in consumer products

### *Information from other countries:*

- (a) Denmark: According to the Danish product register Metilox is found in products on the Danish market in concentrations that can be significant (> 10%). No further information is given due to confidentiality claim.
- (b) Finland: There is no production of this chemical in Finland. In the Finnish product register there are no products containing this substance. It cannot be excluded however, that there are chemical or other products containing the substance as a component.
- (c) Sweden: The chemical was present in the Swedish Chemical Products Register in 1993:

Use of product:	Antioxidant
Tonnes/1992:	Confidential
Branch:	Manufacture of lubricant and engine oils

- (d) Canada: used in  
scavengers/antiscaling agents  
Fragrances/perfumes/deodorisers/flavouring agents.  
Antioxidants/corrosion/tarnish inhibitors/  
Lubricating agents

Reference:	(a)	Niemelä, 1993 (ref 28)
	(b)	Malm, 1993 (ref 27)
	(c)	Wahlström, 1993 (ref 35)
	(d)	Lewis, 1994 (ref 43)

## 1.8 Occupational Exposure Limit Value

There is currently no specific exposure limit for Metilox in the lists of ACGIH (U.S.), OSHA (U.S.), MAK (Germany), OEL (U.K.), MAK (Austria) and MAK (Switzerland). The producer recommends in the MSDS an exposure limit of 5 mg/m<sup>3</sup> TWA (8 hours).

**1.9 Sources of Exposure**

Source: Media of release: Water  
Quantities per media: unknown

Remarks: Switzerland.  
Metilox is produced by reaction of 2,6-di-tert-butylphenol with methyl acrylate. The purified Metilox is converted by transesterification to different commercially available phenolic antioxidants.

**1.10 ADDITIONAL REMARKS****A Options for disposal**

Incineration.

**B. Other remarks**

No other remarks

## 2. PHYSICAL-CHEMICAL DATA

### 2.1 MELTING POINT

Value:	66.1°C
Decomposition:	No
Sublimation:	No
Method:	Ciba internal method IA-123/1
GLP:	No
Reference:	Ciba, 1989a (ref 6)

### 2.2 BOILING POINT

Value:	335.8 °C
Pressure:	at 1013 hPa
Decomposition:	No
Method:	Ciba internal method
GLP:	No
Reference:	Ciba, 1987 (ref 5)

### 2.3 DENSITY

Type:	Relative density
Value:	1.05 g/cm <sup>3</sup>
Temperature:	64 °C
Method:	Ciba internal method
GLP:	No
Reference:	Ciba, 1987 (ref 5)

### 2.4 VAPOUR PRESSURE

Value:	0.005 hPa
Temperature:	67°C
Method:	Ciba internal method; Thermogravimetry
GLP:	No
Reference:	Ciba, 1989b (ref 7)
Value:	0.00002 hPa
Temperature:	25°C
Method:	Ciba internal method; Thermogravimetry
GLP:	No
Reference:	Ciba, 1989b (ref 7)

### 2.5 PARTITION COEFFICIENT LOG<sub>10</sub>P<sub>OW</sub>

log Pow:	5.5
Method:	Calculated
Reference:	Ciba, 1989c (ref 8)
log Pow:	5.91
Method:	Calculated according to Howard & Meylan
Reference:	Computer Program KOWWIN (SRC, 1994a) (ref 31)

**2.6 WATER SOLUBILITY****A. Solubility**

Value:	2.2 mg/l
Temperature:	20°C
Description:	Of low solubility
Analytical method:	HPLC with UV-detection at 280 nm
Method:	EEC Dir. 84/449 A.6 (with HPLC)
GLP:	Yes
Remarks:	pH = 5.8 at test end. At the end of the saturation time most of the test substance was still present as a solid. Therefore it is not expected that hydrolysis has influenced the results.
Reference:	Ciba, 1993 (ref 17)

**B. pH Value, pKa Value**

pH Value:	5.8
Concentration:	At saturation
Temperature:	20°C
Method:	Ciba internal method IA-120/1
GLP:	Yes
Reference:	Ciba, 1993 (ref 17)
pKa value:	not available

**2.7 FLASH POINT** (liquids)

Not applicable.

**2.8 AUTO FLAMMABILITY** (solid/gases)

Value:	370 °C
Pressure:	1013 hPa
Method:	Not specified
GLP:	No
Remarks:	Dust
Reference:	Ciba, 1989d (ref 9)

**2.9 FLAMMABILITY**

No data available

**2.10 EXPLOSIVE PROPERTIES**

No data available

**2.11 OXIDIZING PROPERTIES**

No data available

### **2.13 ADDITIONAL DATA**

No additional data available

### 3. Environmental fate and pathways

#### 3.1 STABILITY

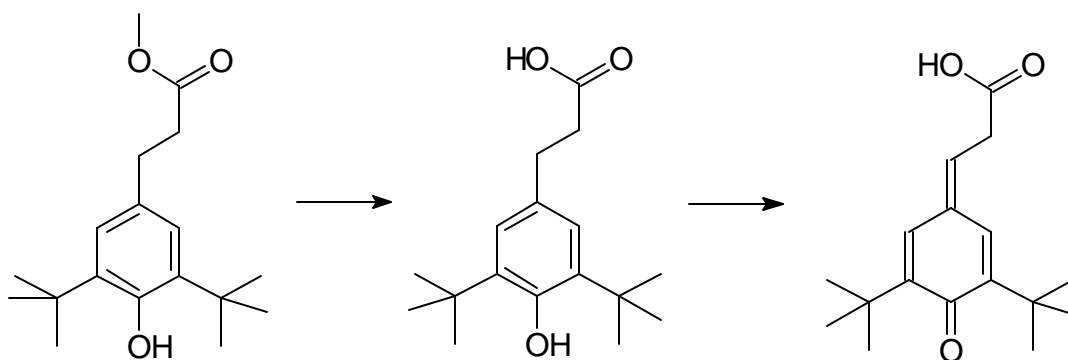
##### 3.1.1 Photodegradation

Type:	Air
Indirect photolysis:	
Type of sensitizer:	OH radicals
Rate constant:	$19.55 \cdot 10^{-12} \text{ cm}^3/\text{molecule} \cdot \text{sec}$
Concentr. of sensitizer:	$5 \cdot 10^5 \text{ radicals/cm}^3$
Degradation:	50% in 19.7 hours (24-hr day)
Method:	Calculated according to Atkinson (1988) Computer program AOPWIN (SRC, 1994b) (ref 32)

##### 3.1.2 Stability in Water

In the Pawtuxet River (Rhode Island, USA) the compound 2,6-tert-butylbenzoquinone-4-(carboxymethyl)methide was found downstream from a small specialty chemicals plant which produces Metilox and several other phenolic antioxidants. Since this compound was not present in the wastewater of this plant it was concluded that the compound was formed by oxidation of Metilox carboxylic acid, the hydrolysis product of Metilox. The acid was likely to be formed by hydrolysis of Metilox.

The methide and the propionic acid group were also formed in an independent experiment by stirring a sediment sample containing various esters of Metilox carboxylic acid in high-purity water for 2 weeks (no details available). Based on these findings it was suggested that the general environmental fate of phenolic antioxidants is their transformation to quinones or quinone methides.



Reference:

Lopez-Avila *et al.*, 1981 (ref 25)

##### 3.1.3 Stability in Soil

No data

### 3.2 MONITORING DATA(environmental)

Type of measurement:	At contaminated site
Media:	Wastewater
Results:	0.6 - 11 ppm
Remarks:	Wastewater from a U.S. specialty chemicals manufacturing plant. Exact location not reported. Years: 1975/76.
Reference:	Jungclaus <i>et al.</i> , 1978 (ref 24).
Type of measurement:	At contaminated site
Media:	Surface water
Results:	0.025 - 0.20 ppm
Remarks:	Receiving water (river) from a U.S. specialty chemicals manufacturing plant. Exact location not reported. Years: 1975/76.
Reference:	Jungclaus <i>et al.</i> , 1978 (ref 24).
Type of measurement:	At contaminated site
Media:	Sediment
Results:	1.5 - 170 ppm
Remarks:	Sediments in the receiving water (river) from a U.S. specialty chemicals manufacturing plant. Exact location not reported. Year: 1976. Tar-like balls (smaller than a pea) consisting entirely of a mixture of anthropogenic compounds were found at two sampling sites and extracted with the sediment.
Reference:	Jungclaus <i>et al.</i> , 1978 (ref 24).

### 3.3 Transport and Distribution

#### 3.3.1 Transport

Type:	Volatility
Media:	Water - air
Method:	Calculated according to Lyman <i>et al.</i>
Results:	Based on a water solubility of 2.2 mg/l and a vapour pressure of 0.002 Pa, the calculated Henry's Law constant is 0.266 Pa · m <sup>3</sup> /mole.
Reference:	Lyman <i>et al.</i> , 1982 (ref 26)
Type:	Adsorption
Media:	soil
Method:	Calculated
Results:	Koc = 22000
Reference:	PCKOC program (v1.66) (ref 45)

#### 3.3.2 Theoretical Distribution (Fugacity Calculation)

Media:	Air-biota-sediment-soil-water
Method:	Fugacity level I
Results:	

Distribution	Compartment	Volumes
0.007 %	Air	$1 \cdot 10^{14} \text{ m}^3$
0.14 %	Water	$2 \cdot 10^{11} \text{ m}^3$
97.6 %	Soil solids	$9 \cdot 10^9 \text{ m}^3$
2.17 %	Sediment solids	$1 \cdot 10^8 \text{ m}^3$
0.068 %	Suspended sediment	$1 \cdot 10^6 \text{ m}^3$
0.0055 %	Biota (fish)	$2 \cdot 10^5 \text{ m}^3$

## Remarks:

Calculation of the theoretical distribution of Metilox in the environment using the FUGMOD model level I, version 1. All the default values were used.

## Input data:

Molecular mass g/mol	292.42
Melting point deg C	66.1
Vapor pressure Pa	0.002
Solubility g/m <sup>3</sup>	2.2
Log octanol-water p-coefficient	5.91

Reference: FUGMOD, 1992 (ref 20)

Media: Air-biota-sediment-soil-water

Method: EQC (level III), release to water 1000 kg/y

## Results:

Compartment	Distribution
Air	8.5%
Water	2.2%
Soil	8.4%
Sediment	89%

## Remarks:

Calculation of the theoretical distribution of Metilox in the environment using the EQC model level III, version 1.

## Input data:

Molecular mass g/mol	292.42
Melting point deg C	66.1
Vapor pressure Pa	0.002
Solubility g/m <sup>3</sup>	2.2
Log octanol-water p-coefficient	5.91

Reference: EQC, version 1.0 (ref 42)

### 3.4 Identification of Main Mode of Biodegrad. in Actual Use

### 3.5 Biodegradation

#### Study 1

Type: Aerobic  
 Inoculum: Non-adapted activated sludge from municipal treatment plant

Preparation of test substance:	Solved in mineral solution using 0.1 mg/l Nonylphenol 10EO5PO as an emulsifier
Concentration:	a) 10.5 mg/l related to test substance b) 22.1 mg/l related to test substance
Medium:	Sewage treatment
Sampling:	day 3, 7, 10, 13, 17, 20, 24, 27, 28
No culture flasks:	2
Controls:	2 aniline references and two blanks
Test temperature:	22 ± 2 °C
Degradation:	a) 8% in 28 days b) 3% in 28 days
Results:	Under test condition no biodegradation observed
ThCO <sub>2</sub> :	4.05 mg CO <sub>2</sub> / mg test substance
Method:	84/449 EEC C.5 (CO <sub>2</sub> evolution test)
GLP:	No
Test substance:	Metilox, purity: techn. grade.
Remarks:	Values are based on nominal concentrations. 0.1 mg/l Nonylphenol 10EO5PO was used as an emulsifier. Precipitates were observed.
Reference:	Ciba, 1989e (ref 10)

## Study 2

Type:	Aerobic
Inoculum:	Mixed from sewage treatment plant, Rhine water and garden soil
Preparation of test substance:	Prepared as the potassium-salt
Concentration:	19.8 mg/l DOC
Medium:	Sewage treatment
Phys. Parameters sampling:	day 7, 14, 17, 21, 25, 29, 32, 34
Phys. data:	pH = 6.9-8.3, dissolved oxygen: 6.5-7.7 mg O <sub>2</sub> /l
DOC sampling:	daily from day 20 - 35
System:	Two small activated sludge plants (OECD 303A); retention time 2h, rate 1l/h; fed with synthetic sewage (=160 mg/l peptone + 110 mg/l meat extract); adapted for 20 days. Sludge d.w. is 1.5-1.9 g/l for the test unit and 1.2-2.1 g/l for the control unit.
Controls:	control unit fed with synthetic sewage
Test temperature:	23 ± 2 °C
Degradation:	Blank: 88.6% DOC of synthetic sewage Test substance: reported as 20.6% DOC. After recalculation a value of 30.5% DOC was found.
Method:	80/303A OECD (Coupled units test)
GLP:	No
Test substance:	Potassium salt of 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionic acid prepared from technical grade Metilox.
Remarks:	<ol style="list-style-type: none"> <li>1. Also the amount of phenol formed as possible degradation product was measured and found to be undetectable.</li> <li>2. Recalculation of the degradation rate gave a result that differed from the one reported by the author (30.5%/20.6%).</li> <li>2. The test was performed with the Potassium salt of 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionic acid and not with Metilox itself.</li> <li>3. A coupled units test is actually an activated sludge plant model in which test substance is continuously fed to the system (kind of adaptation). The degradation percentage can be seen as a best case compared to the OECD 301-tests.</li> </ol>
Reference:	Ciba, 1981 (ref 36)

### 3.6 BOD<sub>5</sub>, COD or Ratio BOD<sub>5</sub>/COD

No data.

### 3.7 Bioaccumulation

Species: Japanese carp (*Cyprinus carpio*)  
Concentration: 0.1 and 1.0 mg/L test substance  
Exposure period: 8 weeks  
Procedure: The carp (24 g, 10 cm) was kept in the aquarium with the test substance under flow through conditions (432 L/day) for a period of 8 weeks. The temperature during the test was 25°C and the oxygen concentration was between 7.1 and 7.4 mg/L. the test waster was analysed once a week and test fish were analysed after 1, 2, 3, 4, 6 and 8 weeks by HPLC.

BCF: For the free acid of metilox: 60-223 at highest concentration and 121-532 at the lowest concentration

Method: OECD 305 C (1981).  
GLP: No data.  
Test substance: Mixture containing 6 different esters of metilox acid (36.5% compound C, 18.6% compound E and 5.6% metilox)

Remarks:  
1. The test was actually set up to determine the bioconcentration factor of compounds C and E. In the test water and in the fish body the free acid of metilox was detected. Bioconcentration factors were tentatively measured and resulted in BCF of 60-223 at 50 µg metilox-acid/L and 121-532 at 5 µg metilox-acid/L.  
2. The information in the report available to the reviewer was essentially confined to the information included in the above summary. It should be stated that the structures of all 6 components of the test substance are available.

Reference: Takamutsu *et al.*, 1978 (ref 46).

### 3.8 Additional Remarks

Based on the mean measured water (0.07 ppm) and sediment (20 ppm) concentration values of Metilox in the vicinity of a U.S. specialty chemicals manufacturing plant, the estimated Sediment Accumulation Factor is 286.

Reference: Jungclaus *et al.*, 1978 (ref 17).

## 4. Ecotoxicological Data

### 4.1 Acute / Prolonged Toxicity to Fish

Type of test: Static  
 Species: Zebra fish (*Brachydanio rerio*)  
 Supplier: West Aquarium (Bad Lauterberg)  
 Number per concentration: 10/replicate; 1 replicate/treatment  
 Size/weight/loading: 20-29 mm/0.07-0.17/0.08 g/l  
 Feeding during test: none  
 Exposure period: 96 hours  
 Dilution water: dechlorinated tap water (178 mg CaCO<sub>3</sub>/l; 23 ± 1 °C)  
 Test concentrations(nominal): 1.0, 1.8, 3.2, 5.8, 10 mg/l  
 Exposure vessel type: 20 l vessels filled with 15 l of water  
 Photoperiod: 16 hours light  
 Measuring times: 0, 24, 48, 72 and 96 h  
 Dissolved oxygen: 87-102%  
 pH: 7.8-8.1  
 Temperature: 23 ± 1°C  
 Test parameters: mortality/symptoms  
 Observation times: 24, 48, 72 and 96 h  
 Mortality (96 h): 0, 0, 0, 70, 90% at diff. Conc.  
 Other effects (96 h): severe swimming behaviour; severe loss of equilibrium; slight to moderate resp. function  
 Dose related effects: yes  
 Results: LC<sub>50</sub> (24h) > 10 mg/l (highest tested conc.)  
 LC<sub>50</sub> (96h) = 5.6 mg/l  
 LC<sub>0</sub> (96h) = 3.2 mg/l  
 LC<sub>100</sub> (96h) > 10 mg/l  
 Analytical monitoring: No  
 Method: OECD 203  
 Statistical method: Berkson, JASA48 (1953), 569  
 GLP: No  
 Test substance: Metilox, purity: tech. grade  
 Remarks:  
 1. No analyses on test substance concentrations were performed. Based on hydrolysis data the effects seen may be caused by metilox or its hydrolysis products.  
 2. Alkylphenol-polyglycol-ether and THF were used to solubilise the test substance. No mortalities were observed in the vehicle (88.7 mg THF and 0.08 mg alkylphenol-polyglycol-ether per liter) in the concentration used for the highest test concentration. The test substance is stated to be homogeneously distributed. From this it is concluded that a suspension or emulsion was tested.  
 3. The LC<sub>50</sub> value derived is above the water solubility of Metilox (2.2 mg/L). Therefore it is concluded that the LC<sub>50</sub> is above the water solubility.  
 Reference: Ciba, 1989f (ref 11)

### 4.2 Acute Toxicity to Aquatic Invertebrates

#### A Daphnia

Type of test: Static

Species:	<i>Daphnia magna</i> Straus
Source:	CIBA-GEIGY, Basel
Number:	
Breeding method:	Cultured in reconstituted water (240 mg CaCO <sub>3</sub> /l), 16h light ( $\pm$ 1500 lux), 20 $\pm$ 1 °C)
Age:	0-24 h
Feeding (pretreatment):	thrice weekly a combination of green algae and a Tetramin suspension
Feeding during test:	none
Exposure period:	24 hours
Test concentrations:	0.32, 0.58, 1.0, 1.8, 3.2, 5.8, 10, 18, 32, 58 and 100 mg/l
Exposure vessel type:	Covered beakers containing 100 ml solution
Number of individuals:	5 per replicate; 4 replicates/treatment
Physical measuring:	At 0 and 24 h oxygen, pH and temperature
Dissolved oxygen:	94-103%
pH:	7.6-7.7
Temperature:	20-21°C
Results:	EC <sub>50</sub> (24h) > 100 mg/l EC <sub>0</sub> (24h) = 5.8 mg/l EC <sub>100</sub> (24h) > 100 mg/l
Mortality:	0, 0, 5, 0, 0, 0, 10, 5, 20, 30, 40% Analytical monitoring: No
Method:	OECD 202
GLP:	No
Test substance:	Metilox, purity: tech. grade
Remarks:	
	1. Values are based on nominal concentrations. Tween 20 was used to solubilise the test substance. A slight deposit was observed at concentrations 5.8 - 100 mg/l (nominal) from the start of the test. 5 % immobilization was observed in the vehicle (4 mg/l Tween 20).
	2. The EC <sub>50</sub> value derived is above the water solubility of Metilox (2.2 mg/L). Therefore it can only be concluded that the EC <sub>50</sub> is most probably above water solubility.
Reference:	Ciba, 1989g (ref 12)

## B. Other aquatic organisms

No data available.

### 4.3 Toxicity to Aquatic Plants, e.g. algae

Species:	<i>Scenedesmus subspicatus</i>
Controls:	Blank: water
Initial cell concentration:	11700 cells/ml
Test medium:	According to the guideline cited
Exposure vessel type:	100 ml Erlenmeyer flasks (stoppered) containing 50 ml test solution
Number of replicates:	3/treatment (6 for blank control)
Endpoint:	Biomass
Exposure period:	72 hours
Photoperiod:	continuous; 120 $\mu$ E/m <sup>2</sup> sec ( $\pm$ 8000 lux)
Shaken:	continuous
Physical measuring:	At 0 and 72 h pH and temperature
pH:	7.8-10.8
Temperature:	23 $\pm$ 1°C
Measurement cell density:	TOA cell counter; at 24, 48 and 72 hrs



## Remarks:

Temperature: 20 ± 2°C.

Values are based on nominal concentrations. The substance was directly added to the test medium.

Reference substance 3,5-dichlorophenol: EC<sub>50</sub> (3h) = 14 mg/l.

Reference: Ciba, 1989h (ref 13)

## 4.5 Chronic Toxicity to Aquatic Organisms

### 4.5.1 Chronic Toxicity to Fish

No data available

### 4.5.2 Chronic Toxicity to Aquatic Invertebrates

Type of test:	Semi-static (renewal every 48 hours)
Species:	<i>Daphnia magna</i> Straus
Endpoint:	Mortality and Reproduction rate
Exposure period:	21 days
Test concentrations:	nominal: 0.16, 0.30, 0.56, 1.0, 2.2 measured: 0.12, 0.17, 0.37, 0.57, 1.14
Results:	Parental immobility: EC <sub>50</sub> (21d) = 0.97 mg/l Reproduction: EC <sub>50</sub> (21d) = 0.59 mg/l NOEC = 0.123 mg/l LOEC = 0.367 mg/l
Analytical monitoring:	HPLC with UV detection at 230 nm
Method:	OECD 202, part II (1991)
GLP:	Yes
Test substance:	Metilox, purity: > 98%

*Experimental design:* 10 vessels per concentration were used each containing one neonate (< 24hrs old) daphnid in 50 ml M4 test medium (hardness 250 mg CaCO<sub>3</sub> mg/l; pH8. The control groups (0 mg/l and solvent-control) consisted each of 20 daphnids. The test solutions were renewed every two days. Stock solutions were prepared in methanol. At the start of the test and at each renewal the condition of the parental daphnia was recorded and during the reproduction phase the number of living offspring, immobile young and number of unhatched eggs were recorded.

*Light:* 16 hours photoperiod daily, 600 lux.

*Feeding:* Defined volumes of different *Chlorella pyrenoidosa* suspensions were added daily (except on day 11).

*Controls:* 1. Test medium without test substance or any other additives 2. Test medium without test substance but with the additive used in the treatment of the stock solutions (methanol, 0.1ml/l).

*Results:*

Mortality/immobility after 21 days: (%)

At 0, 0 (vehicle), 0.12, 0.17, 0.37, 0.57 and 1.14: 10, 5, 20, 0, 22, 20 and 60%

Mean number living young on day 21:

At 0, 0 (vehicle), 0.12, 0.17, 0.37, 0.57 and 1.14: 161, 164, 158, 138, 111, 80.9, 40.3.

Measured concentrations were 52-77% of nominal. All test solutions were clear. There was no indication of precipitation of the test material.

Temperature: 19.5-21.5°C / pH 7.6-8.7 / Oxygen concentrations: 7.0-9.6 mg/l

Reference: NOTOX, 1995 (ref 29)

## 4.6 Toxicity to Terrestrial Organisms

### 4.6.1 Toxicity to soil dwelling organisms

No data available.

### 4.6.2 Toxicity to terrestrial plants

Species: a) Ryegrass (*Lolium perenne*)  
 b) Turnip (*Brassica rapa*)  
 c) Vetch (*Vicia sativa*)

Soil: 78% „Loess“ and 22% fine quartz sand (pH = 7.4;  
 carbon content 0.24%; percent particles < 20 µm  
 not determined)

Endpoint: Emergence; Growth

Exposure period: 19 days

Procedure:

The test substance was mixed with dry quartz sand and subsequently mixed with the dry soil. Treatment concentrations were 1, 10 and 100 mg/kg dry soil. Aliquots of 350 g (d.w.) of soil were filled into plastic pots and into each pot 5 seeds of a particular test species were planted. Each species and concentration was tested with 4 replicate pots. The pots were placed in a growth chamber (16 h light (2600-3600 Lux), 8 h dark, 24 ± 1°C). Water losses were compensated on working days. The test duration was 19 days (2-3 days until 50% of the control seedlings had emerged, and 16-17 days afterwards. On day 16 post-emergence, the wet weight of the surviving plants was determined (day 17 for turnip).

#### Results:

Emergency inhibition as % inhibition of the emergency of plants on day 1-8 compared to control treatment:

Conc. mg/kg	Inhibition % a	Inhibition % b	Inhibition % c
1	11	0	17
10	-5	-5	-11
100	5	-5	0

Growth inhibition as % inhibition of plant weight at the study end compared to the control treatment:

Conc. mg/kg	wet			dry		
	a	b	c	a	b	c
1	-25	-333	-173	-24	-151	-189
10	-51	-207	-66	-63	-100	-66
100	-120	-484	-243	-124	-271	-258

**Conclusion:**

	Emergence (LC <sub>50</sub> )	Duration <sup>1)</sup>	Growth (EC <sub>50</sub> (16-17d)) <sup>2)</sup>
a)	> 100 mg/kg	3 days	> 100 mg/kg
b)	> 100 mg/kg	2 days	> 100 mg/kg
c)	> 100 mg/kg	3 days	> 100 mg/kg

1) Number of days until 50% of the seedlings have emerged in the blank

2) 16-17 days after 50% of the seedlings have emerged in the blank

Method: OECD 208 (1984)

GLP: No

Test substance: Metilox, purity: tech. grade

Remarks:

1. Values are based on nominal concentrations (mg/kg dry weight of soil).

2. No phytotoxic effects were observed on all three species.

3. The test substance shows a stimulated effect on the plant growth, which may lead to morbid growth of weeds when the substance comes into the environment.

Reference: Ciba, 1989i (14)

**4.6.3 Toxicity to other non mammalian terrestrial species**

No studies located.

**4.7 BIOLOGICAL EFFECTS MONITORING (including Biomagnification)**

No information available.

**4.8 BIOTRANSFORMATION AND KINETICS**

No data available.

**4.9 ADDITIONAL REMARKS**

No additional remarks.

## 5. TOXICITY

### 5.1 ACUTE TOXICITY

#### 5.1.1 Acute Oral Toxicity

Type:	LD <sub>50</sub>
Source:	Ciba Geigy, Basle
Age:	7-8 weeks
Species/strain:	Rat / Tif:RAIf (SPF)
Number:	5 male/ 5 female
Initial body weight:	male: 174 g; female: 167 g
Volume administered:	20 ml/kg
Value:	> 5000 mg/kg body weight
Method:	EPA 1978
GLP:	No
Test substance:	Metilox, purity: not specified
Results:	<p>No deaths occurred after a single dose of 5000 mg/kg body weight within the observation period of 2 weeks.</p> <p>Clinical symptoms: moderate to slight dyspnoea until day 7; moderate ruffled fur until day 9 and slight exophthalmos and curved body position. All animals recovered within 10 days.</p> <p>Autopsies: No compound related gross organ changes were observed.</p>
Reference:	Ciba, 1981 (ref1)

#### 5.1.2 Acute Inhalation Toxicity

Type:	LC <sub>50</sub>
Species/strain:	Rat / Charles River
Number:	5 male/ 5 female
Initial body weight:	male: 266 g; female: 193 g
Type of exposure:	whole body
Exposure time:	4 hours
Concentration measured:	55.5 mg/m <sup>3</sup> (25 °C; 76.0 mm Hg)
Value:	LC <sub>50</sub> (4h) > 55.5 mg/m <sup>3</sup>
Method:	Not indicated (used as range finding test)
GLP:	No
Test substance:	Metilox, purity: not specified
Procedures and results:	<p>A group of 10 rats was exposed to the dust of the test substance for 4 hours in a 70-liter chamber. The average analytical dust concentration was 55.5 mg/m<sup>3</sup> air; this was measured by dividing the amount of dust collected on a glass fiber filter by the total volume of air drawn through the filter during the sampling period. After exposure, all test animals were observed for 14 days and then necropsied.</p> <p>No deaths, no treatment related effects on body weight, no clinical symptoms and no gross organ changes were observed.</p> <p>4.5 % of total compound was in particle size &lt; 10 µm.</p>
Reference:	IBT, 1974 (ref 22)

#### 5.1.3 Acute Dermal Toxicity

Type:	LD <sub>50</sub>
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Species/strain:	Rabbit / New Zealand
Number:	3 male
Initial weight:	2.65 kg
Value:	LD <sub>50</sub> > 3000 mg/kg
Method:	Range-finding study Single doses of 300, 1000 and 3000 mg/kg were applied to the abraded skin of one male per dose.
GLP:	No
Test substance:	Irganox 1300 (=Metilox), purity: not specified
Procedures and results:	No mortality, no gross organ changes. Some pustules were noted in the rabbits of all dose levels at 7 days and slight desquamation was observed in all animals after 14 days. One animal decreased in body weight from 2.56 kg to 2.44 kg after 14 days.
Remarks:	The size of the treated area is not specified nor is the dose given.
Reference:	IBT, 1975 (ref 23)

### 5.1.4 Acute Toxicity, Other Routes of Administration

No data available

## 5.2 Corrosiveness / Irritation

### 5.2.1 Skin Irritation / Corrosion

Species/strain:	Rabbit / New Zealand White
Source:	Kleintierfarm Madörin
Number:	3 male/3 female
Total volume applied:	0.5 mg
Area of exposure:	6.25 cm <sup>2</sup>
Examination time points:	24, 48, 72 hrs, 4, 7 days
Results:	Not irritating
Method:	EPA, CFR 43, No. 163, August 22, 1978
GLP:	No
Test substance:	Metilox, purity: not specified
Procedures and results:	The test substance was applied under occlusion for 24 hours. The scoring was according to Draize. The test substance was found to cause minimal irritations when applied to intact and abraded rabbit skin. The calculated primary irritating index was 0.6.
Remarks:	<ol style="list-style-type: none"> <li>1. OECD guidelines require an application period of 4 hour and the use of a semi-occlusive dressing. A 24-hour application period under occlusion can be considered to represent a worst case scenario.</li> <li>2. No bodyweights mentioned.</li> </ol>
Reference:	Ciba, 1982a (ref 2)

### 5.2.2 Eye Irritation / Corrosion

#### Study 1:

Species/strain:	Rabbit / New Zealand White
-----------------	----------------------------

Number: 3 male/3 female  
 Amount instilled: 0.5 mL  
 Control: other eye untreated  
 Examination on: day 1, 2, 3, 4 and 7  
 Tool used to assess score: slitlamp  
 Results: Not irritating  
 Method: EPA, CFR 43, No. 163, August 22, 1978  
 GLP: No  
 Test substance: Metilox, purity: not specified

**Procedures and results:**

The test was performed with and without rinsing of the eyes after 24 hours. The substance was found to cause minimal irritation when applied to the rabbit eye mucosa (only in one animal redness of the conjunctiva was observed on day 1). The primary irritation index was found to be 0.1 for unrinsed eyes and 0.0 for rinsed eyes.

Reference: Ciba, 1982b (ref 3)

**Study 2:**

Species/strain: Albino Rabbit  
 Number: 3 animals; sex not specified  
 Amount instilled: 100 mg undiluted  
 Examination after: 1, 24, 72 hours and 7 days  
 Results: not irritating: Irritating  
 Method: not specified, no rinsing of the eye  
 GLP: No  
 Test substance: Irganox 1300, purity: not specified

**Results:**

All three animals showed an initial redness (2), chemosis (2) and discharge (3) of the conjunctiva, which disappeared completely within 72 hours.

Reference: IBT, 1974 (ref )

### 5.3 Skin Sensitisation

Type: Patch test  
 Species/strain: Human  
 Results: Not sensitizing  
 Classification: Not sensitizing  
 Method: Shelanski Repeated Insult Patch Test  
 GLP: No  
 Test substance: Metilox, purity: not specified

**Remarks:**

Tested at a 0.5% solution in dimethyl phthalate on 50 human volunteers.

Number with skin reaction at challenge: none.

Number with skin reaction in control group at challenge: no control group.

Reference: IBL, 1965 (ref 21)

### 5.4 Repeated Dose Toxicity

Species/strain: Rat / Wistar  
 Sex: Male/Female  
 Body weight: 42-59 g (males), 43-59 g (females)  
 Route of administration: Oral feed  
 Exposure period: 28 days  
 Frequency of treatment: Daily

Post exposure observ. period: None  
 Dose: 0.2, 1.0 and 5.0%, resulting in 220, 660 and 585 mg/kg bw/day (for males 220, 760 and 585 mg/kg bw/day and for females 216, 562 and 585 mg/kg bw/day)

Number of animals: 5/sex/dose group  
 Control group: Yes, concurrent no treatment  
 LOAEL: 220 mg/kg body weight/day, based on liver enlargement  
 GLP: No  
 Test substance: Metilox, purity: not specified  
 Method:

5 male and 5 female rats per group were fed with a standard diet containing 0, 2000, 10000 and 50000 ppm of Metilox resulting in a mean daily intake of 0, 220, 660 and 585 mg/kg body weight. Observations were made on body weight (weekly), food intake (during whole experimental period), water intake (first week) and clinical signs and mortality.

At necropsy animals were macroscopically examined for pathological changes, liver and kidneys were weighed and examined microscopically.

#### Results:

All animals in the high dose group died in the second week after having lost about 30% of body weight in parallel to a reduced consumption of food. One female at 660 mg/kg died in the fourth week. At 660 and 585 mg/kg all rats had very unhealthy appearance within a few days.

Intermediate and high dose group animals showed reduced food and increased water consumption and, as a consequence, reduced body weight gain.

The relative liver weight was increased in all dose groups and in both sexes in a dose dependent manner. Relative kidney weights were increased in females of the intermediate dose group (no measurement in the high dose group).

Gross pathology revealed stercoraceous stools, severe emaciation and distended abdomens at 660 mg/kg. Involuntary discharge of urine was seen at this dose level, as well as greatly enlarged, dark-brown coloured liver. In one female at 660 mg/kg severe pneumonia and splenic enlargement was seen. At the lowest dose level livers were slightly enlarged, but not discoloured.

Microscopic examination revealed hepatic damage, consisting of homogenous cytoplasm of hepatocytes, often containing large eosinophilic droplets, hepatocytic nuclei varying in size and chromatin pattern and an increased number of binucleated cells and mitotic figures at 660 mg/kg. Renal damage in the females at 660 mg/kg consisted of dilatation of cortical and medullary tubules lined by flattened epithelium and often filled with cellular debris.

#### Remark:

1. The rats used were very small (~50 g) and according to standard growth data about 20 days old when the study was started.
2. Intake in mg/kg bw was calculated by the reviewer based on bodyweights and food intake mentioned in the report. The actual intake in the high dose group was very low due to the very low food intake in this group.
3. The number of endpoints investigated is very limited (study is a range finding study).

Reference: TNO, 1968 (ref 33)  
 Species/strain: Rat / Wistar  
 Sex: Male/Female  
 Mean body weight: 57.3-57.7 (males), 51.8-52.1 (females)  
 Route of administration: Oral feed  
 Exposure period: 90 days  
 Frequency of treatment: Daily  
 Post exposure observ. period: None  
 Dose: 0.04, 0.2 and 1.0% in oral feed, resulting in 70, 140 and 700 mg/kg bw/day for males and females

Number of animals: 10/sex/dose group  
 Control group: Yes, concurrent no treatment  
 LOAEL: 70 mg/kg bw/day (males);  
 GLP: No  
 Test substance: Metilox, purity: not specified

Method:

10 males and 10 females per group were fed 0, 400, 2000 and 10000 ppm of the test article corresponding to an estimated daily intake of 70, 140 and 700 mg/kg bw/day for males and females. Individual body weights were monitored weekly, food intake was determined during week 1-4 and 11 and 12. Haematologic data (hemoglobin, packed cell volume, erythrocyte count and total and differential leukocyte count) were collected in week 12. Serum-pyruvic transaminase, serum glutamin-oxaloacetic transaminase, serum alkalinephosphatase, serum ornithine carbamyl transferase and total serum protein were determined at the end of the experiment. At sacrifice, animals were examined macroscopically and the following organs were weighed: heart\*, liver\*, kidney\*, spleen, brain, testes\*/ovaries\*, thymus\*, pituitary, thyroid\* and adrenals\*. These organs were also examined microscopically in high dose and control animals, plus the following organs: lung, salivary glands\*, esophagus, Harderian gland, stomach\*, small and large intestine, trachea, skeletal muscle, aorta, exorbital lacrimal gland, axillary and mesenteric lymph nodes, pancreas, skin, urinary bladder, bone marrow, prostate, epididymis, coagulating gland, seminal vesicle, preputial gland, uterus\*, spinal cord and femoral nerve. \* marked organs were also examined at lower dosage levels.

Results:

At the highest dose 80% of males and 60% of females died, most during the second and third week.

Surviving animals in the highest dose group were small and emaciated. Body weight was reduced, as well as food and water consumption.

Blood parameters:

Leucocyte counts and hemoglobin content were decreased in the highest dose group, while levels of Serum Alkaline Phosphatase (ALP) were highly increased, rendering the evaluation of the group findings difficult. Serum glutamic-oxaloacetic transaminase was decreased in the high and intermediate dose group, showing significance in females only. The latter finding is not considered biologically significant.

Necropsy findings:

At the high dose level, most relative organ weight were increased, probably due to the decreased body weights. At the intermediate level, relative liver, brain and thyroid weights (also at the lowest dosage) were increased in males, in females only relative liver weight was increased significantly.

Livers at this dosage were enlarged and dark-brown, thyroids were enlarged. Severe pulmonary emphysema and atrophy of testicles, prostate and seminal vesicle was seen in one male at the high dose level.

Microscopic changes were found mostly in the liver and thyroid: (in highest dose group) in the liver enlarged hepatocytes were seen with homogenous cytoplasm containing large, eosinophilic droplets, further, variations in size and chromatin pattern of hepatocytic nuclei, an increased number of binucleated cells, necrosis of individual parenchymal cells and slight proliferation of bile ducts were noted. In the intermediate dose group only slightly homogenous cytoplasm and nuclei varying slightly in size were seen. Thyroid: activated appearance (dose-dependent), resembling a thyroid of rats given thyroid-stimulating hormone; metilox appeared to have a goitrogenic effect of which signs were already visible in the lowest dose group.

Further changes were found at the highest dose level in the kidney (fatty infiltration, pigmentation, cystic tubules), male and females genital organs (atrophic changes),

lung (edema and emphysema), stomach (hyperkeratosis), adrenal (fatty 'vacuoles', hyperemia and distended sinusoids), bone marrow (hypoplasia) and submaxillary salivary gland (increased ratio ducts:acini), these changes were at least in part compound-related.

Remark:

1. The actual intake levels were calculated by the reviewer based on an estimation of mean food intake of 17.5 g/rat for male rats and 12.5 mg/rat for female rats and mean body weights of 250 g and 175 g resp. Data in the report were insufficient to base the calculation upon.
2. The rats used were very small (~50 g), it is doubted whether the animals were young adults.

Reference: TNO, 1969 (ref 34)

## 5.5 Genetic Toxicity In Vitro

### A. Bacterial Test

Type:	Ames test												
System of testing:	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538												
Concentration:	20, 80, 320, 1280 and 5120 µg/plate												
Vehicle:	acetone												
Number of replicates:	3												
Metabolic activation:	With and without												
Metabolic activation system:	Rat liver S9-mix (Aroclor 1254 induced)												
Positive controls:	Daunorubicin-HCl (TA98), 4-nitroquinoline-N-oxide (TA100), N-methyl-N'-nitrosoguanidine (TA1535), aminoacridine (TA1537) and 2-nitrofluorene (TA1538)												
Negative controls:	vehicle												
Method:	According to Ames, direct plating												
GLP:	No												
Criteria for evaluating results:	The test substance is considered not mutagenic if the number of revertant colonies is not doubled in relation to the negative control at any concentration.												
Results:	Negative												
Cytotoxicity conc:	With metabolic activation: 5120 µg/plate Without metabolic activation: 1280 µg/plate												
Precipitation conc:	5120 µg/0.1 ml												
Genotoxic effects:	<table> <thead> <tr> <th></th> <th>+</th> <th>?</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>With metabolic activation</td> <td>[ ]</td> <td>[ ]</td> <td>[x]</td> </tr> <tr> <td>Without metabolic activation</td> <td>[ ]</td> <td>[ ]</td> <td>[x]</td> </tr> </tbody> </table>		+	?	-	With metabolic activation	[ ]	[ ]	[x]	Without metabolic activation	[ ]	[ ]	[x]
	+	?	-										
With metabolic activation	[ ]	[ ]	[x]										
Without metabolic activation	[ ]	[ ]	[x]										
Test substance:	Metilox, purity: >99%												
Reference:	Ciba, 1983 (ref 4)												

### B. Non-Bacterial in Vitro Test

Type:	Cytogenetic assay
System of testing:	Cell line CCL 61 (Chinese hamster ovary cells)
Concentrations:	2.44, 4.88, 9.77 and 19.53 µg/ml without activation; higher concentrations could not be scored due to

	cytotoxicity 19.53, 39.06, 78.13 and 156.25 µg/ml with activation
Metabolic activation:	With and without
Metabolic activation system:	Rat liver S9-mix (Aroclor 1254 induced)
Exposure time:	Without metabolic activation: 18 hrs or 42 hrs; with metabolic activation: 3 hrs, followed by 15 or 39 hrs recovery
Positive controls:	Mitomycin C (without activation), cyclophosphamide (with activation)
Negative controls:	Historical
Nr. of metaphases scored:	200
Number of replicates:	2
Method:	OECD 473 (1983)
GLP: Yes	
Criteria for evaluating results:	For a positive result the percentage of aberrations in a treatment group is higher than 6.0 and differs statistically significant from the negative control value.
Statistics:	Chi-squared test
Results:	Negative
Cytotoxicity conc:	With metabolic activation: 156.25 µg/mL Without metabolic activation: 19.35 µg/mL
Precipitation conc:	not observed
Test substance:	Metilox, purity: >98%
Reference:	Ciba, 1994 (ref 18)

## 5.6 GENETIC TOXICITY IN VIVO

No studies available.

## 5.7 Carcinogenicity

No data available.

## 5.8 Toxicity to Reproduction

Type:	Reproduction/Developmental Screening Test
Species/strain:	Rat / Tif: RAI f (SPF)
Source:	Animal Production, Switzerland
Sex:	Male/Female
Age:	15-16 weeks (males), 10-11 weeks (females)
Number of animals:	15/sex/dose group
Mean body weights:	457-460 g (males), 235-239 g (females)
Route of administration:	Oral (gavage)
Vehicle:	CMC (0.5%)
Frequency of treatment:	Daily
Post exposure observation period:	None
Premating exposure period:	2 weeks
Duration of exposure:	Males until successful mating and 2 weeks thereafter Females during the whole test period
Duration of the test:	From 2 weeks pre-mating to 4 days post partum
Doses:	10, 100, 250 mg/kg body weight

Control group: Yes, concurrent vehicle  
 Method: OECD 421, Draft updated guideline (1994)  
 GLP: Yes  
 Mating procedures: 1 male/1 female during maximum 14 days. Day of post coitum is defined the day of presence of a vaginal plug or the presence of sperm.  
 Parental observations and measurements:  
 Clinical signs and mortality (daily); body weight (daily); food consumption (weekly pre-mating, days 0, 7, 14 and 21 postcoitum and days 0, 4 postpartum); macroscopy (main organs of thoracic and abdominal cavities, number of corpora lutea in each ovary, number of implantation sites per uterus); organ weight and histopathology (liver, ovaries, testes and epididymes) in control and high dose animals (liver in all dose groups).  
 Offspring observations and measurements:  
 Clinical signs and mortality (daily); no. of live young, sex, litter size and weight (days 0 and 4 postpartum); macroscopic examination of main organs of the thoracic and abdominal cavities.  
 Statistics used ANOVA, Dunnett's t-test, Chi-square, Fischer's exact test, Kruskal-Wallis and Mann-Whitney U-test.

#### Results:

##### **Parental Toxicity**

There were no treatment-related mortalities (1 control male and 1 female at 100 mg/kg bw died). There was an increased incidence of adult males and females in the 250 mg/kg group which displayed discomfort after test substance application for one to four days (pushing head through bedding).

Body weights and food consumption were reduced at 250 mg/kg in males during the first week of the treatment. In females at 250 and 100 mg/kg, these parameters were reduced during pre-mating, gestation and lactation (at 100 mg/kg body weight gain was incidentally reduced during the test period).

##### **Fertility and Reproductive Effects**

Mating, fertility, gestation and parturition indices were unaffected by treatment. All females delivered live pups.

Fertility index was 100% for all dose groups for males and females.

##### **Litter Indices**

Litter size at birth was slightly reduced at 250 mg/kg and number of stillbirths was increased. In the same dose group, pup viability on day 4 post partum and mean pup weights were reduced.

##### **Pathology**

There were no treatment-related macroscopical findings at terminal necropsy for pups. Pups that died showed autolysis.

Treatment-related macroscopical findings in parent animals were limited to an enlarged liver in one high dose group male. However, mean absolute and relative liver weights were increased at 100 and 250 mg/kg (males and females). Subsequently, histopathology of the liver showed an increased incidence of hypertrophy of the hepatocytes in both sexes at 100 and 250 mg/kg. This change was accompanied by cytoplasmic inclusion bodies, more pronounced in males. An increased incidence of cholangiofibrosis of the intrahepatic bile ducts was observed for both sexes at 250 mg/kg and for males at 100 mg/kg.

NOAEL Parental: 10 mg/kg based on decreased body weight and food consumption and liver effects  
 NOAEL F1 Offspring: 100 mg/kg based on reduced body weight gain and viability  
 Test substance: Metilox, purity: >98%  
 Reference: Ciba, 1996 (ref 19)  
 Type: Range finding one-generation study  
 Species/strain: Rat / Tif: RAI f (SPF)

Source: Animal Production, Switzerland  
Sex: Male/Female  
Age: 13-14 weeks (males), 8-10 weeks (females)  
Number of animals: 5/sex/dose group  
Mean body weights: 409-436 g (males), 228-246 g (females)  
Route of administration: Gavage (10 mL/kg bw)  
Vehicle: 0.5% w/w aqueous solution of sodium carboxymethylcellulose in  
0.1% w/w Tween 80.  
Frequency of treatment: Daily  
Post exposure observation period: None  
Premating exposure period: 2 weeks  
Duration of the test: From 2 weeks pre mating to 14 days post coitum  
Doses: 50, 250 and 500 mg/kg body weight  
Control group: Yes, concurrent vehicle  
Method: OECD 421

Method:

5 males and 5 females per dose group were exposed to test substance 14 days prior to mating. For mating, each female was placed with a single male until the day positive mating was observed (as determined by vaginal plug or positive vaginal smear) or for a maximum of 14 days. Dams were necropsied on day 14 post coitum and then males were necropsied.

Mating and fertility indices were calculated for males and females. Clinical signs, mortality and body weight were recorded daily. Feed consumption was calculated weekly (pre mating) and on days 0, 7 and 14 postcoitum. At necropsy a macroscopic examination of the main organs of the thoracic and abdominal cavities was performed, number of corpora lutea in each ovary was counted, as well as number of implantation sites per uterus.

Statistical procedures used were: ANOVA, Dunnett's t test, Chi-Square test, Kruskal-Wallis and Mann-Whitney U-test.

Results:

No parental mortalities occurred. At 250 and 500 mg/kg all males displayed discomfort after administration of test substance, both males and females showed piloerection, hunched posture and reduced activity 1-5 hours after test substance administration, probably due to a pharmacological effect of the compound.

Male body weights were reduced dose dependently at 250 and 500 mg/kg (non-significant); body weight gain in week 1 was reduced dose dependently at 250 and 500 mg/kg (for latter dose significant during the whole treatment period). Female body weights were reduced at 500 mg/kg (significant on several days of week 2), at 250 mg/kg only during gestation (non significant); body weight gain was reduced dose dependently at 250 and 500 mg/kg in week 1.

Feed consumption was reduced dose dependently at 250 and 500 mg/kg for females throughout treatment and for males during week 1.

Mating and fertility indices were between 75 and 100% in all groups. All females were mated except one at the highest dose level. At 250 mg/kg 1 female and at 500 mg/kg 2 females appeared non-pregnant.

There were no compound-related necropsy findings; one male had mottled lung (incidental finding).

Conclusion:

At dose levels toxic to the parent animals, no effects on reproduction were observed.

NOAEL (parental effects): 50 mg/kg, based on changes in body weight (gain)

NOAEL (reproduction): 500 mg/kg, as no effects were seen at doses 50-500 mg/kg

Remark: The test is a range finding test and therefore only 5 animals per sex per dose were used (10/sex/dose are recommended (OECD 421)). The test duration was too short, as animals were sacrificed before partition. Accordingly, no data on offspring are available.

Test substance: CAS 6386-38-5 (Metilox), purity >98%

Reference: Ciba, TK 10027 (Metilox): Rangefinding rat reproduction toxicity screening test, 1994 (ref 38)

## 5.9 Developmental Toxicity / Teratogenicity

No data available.

## 5.10 Other Relevant Information

### A. Specific toxicities

No data available.

### B. Toxicodynamics, toxicokinetics

Type: Metabolism  
 Method: Ciba internal method  
 GLP: No  
 Remarks:  
 Hydrolysis *in vitro* and *in vivo*.

At nearly physiological pH of 7.4 and at a test concentration of 200  $\mu$ M Metilox was rapidly hydrolysed *in vitro* by 0.1% and 0.25% rat serum as well as 1% rat liver homogenate with hydrolysis half-times  $T_{1/2}$  of 13.4, 6 and 12 minutes, respectively. Hydrolysis by 2.5% small intestine homogenate was much slower. The hydrolysis product has been identified as the corresponding carboxylic acid (CAS No. 20170-32-5) by co-chromatography of an authentic [ $^{14}$ C]-labelled reference sample.

[ $^{14}$ C]-Metilox was orally administered to 2 male, starved rats at doses of 9.6 and 8.6 mg/kg b.w. The rats absorbed the compound rapidly as judged by the maxima of radioactivity measured in the blood at 2 and 6 hours after treatment, respectively. One rat experienced a second maximum at 10 hours past treatment.

The predominant metabolite, measured as early as 15 minutes after treatment, was the carboxylic acid, representing 94% of the total radioactivity in the blood, whereas the parent compound represented ~2.5% of the total radioactivity.

Reference: Ciba, 1991b (ref 16)

Type: Absorption, distribution and excretion *in vivo*  
 (ADE-study)  
 Method: US FDA, Bureau of food, 1982  
 GLP: Yes  
 Remarks:

Male Wistar rats (5/treatment) were treated orally (single dose by gavage) with 1 or 10 mg/kg body weight of [ $^{14}$ C]-Metilox and the radioactivity was followed in urine, faeces, blood, plasma, organs and tissues in various experiments. The following excretion pattern was obtained:

Excretion	Treatment: 1 mg/kg b.w.	Treatment: 10 mg/kg b.w.
urine, after 48 hours	32.1 %	33.7 %
urine, after 168 hours	38.7 %	41.5 %
faeces, after 168 hours	53.8 %	58.0 %
Residue in organs		
liver	below limit of quantification	0.103 µg/g
intestinal tract	0.003 µg/g	0.037 µg/g
blood	0.006 µg/g	0.089 µg/g
plasma	0.007 µg/g	0.084 µg/g
other organs/tissues	below limit of quantification	below limit of quantification
Residue in carcass at 168 hours	0.002 µg/g	0.020 µg/g
Overall recovery at 168 hours	96.77 %	102.15 %

Kinetics	Treatment: 1 mg/kg b.w.	Treatment: 10 mg/kg b.w.
Maximum concentration in blood and plasma	after 30 min	after 30 min after 8 hours (2nd maximum)
Elimination half life in blood and plasma	6.6 and 6.4, resp.	10.5 and 7.9, resp.

Reference: RCC, 1990

### 5.11 Experience with Human Exposure

No information available.

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