15. Pesticides

15.1 Introduction

The evaluation of the health effects of pesticides was based on reviews of all available relevant information, including unpublished proprietary data developed by manufacturers of pesticides. The fact that pesticide manufacturers made available to the review groups their proprietary toxicological information on the products under discussion is gratefully acknowledged.

For the sake of completeness, these unpublished studies are included in the reference lists of the monographs as appropriate. Copies of the reports may be requested directly from the manufacturers; they are not available from WHO.

It should be noted that the recommended guideline values for pesticides in drinking-water are set at a level to protect human health; they may not be suitable for the protection of the environment or aquatic life.

It is recognized that the environmental degradation products of pesticides may be a problem in drinking-water. In most cases, however, the toxicities of these degradation products have not been taken into consideration in these guidelines, as data on their identity, presence, and biological activity are inadequate.

15.2 Alachlor

15.2.1 General description

Identity

CAS no.: 15972-60-8
Molecular formula: C₁₄H₂₀ClNO₂

Alachlor is the common name for 2-chloro-N-(2,6-diethylphenyl)-N-methoxymethylacetamide.

Physicochemical properties (1,2)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>White crystalline solid at 23 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>242 mg/litre at 25 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>2.9 × 10⁻³ Pa at 25 °C</td>
</tr>
<tr>
<td>Log octanol-water partition</td>
<td>2.6-3.1</td>
</tr>
</tbody>
</table>

Organoletic properties

Taste and odour thresholds in water of 33 and 110 mg/litre, respectively, have been reported (1).

Major uses

Alachlor is used pre- or early post-emergence to control annual grasses and many broad-leaved weeds mainly in maize, but also in cotton, brassicas, oilseed rape, peanuts, radish, soy beans, and sugar-cane (2).

Environmental fate

Alachlor dissipates from soil mainly through volatilization, photodegradation, and biodegradation (3-5).
Many metabolites have been identified; diethylaniline, detected in some soil studies, interacts rapidly with humic substances in the soil (3). A half-life in soil of 7-38 days has been reported (6). Under certain conditions, alachlor can leach beyond the root zone and migrate to groundwater (1,3).

15.2.2. Analytical methods

Water samples are extracted with chloroform, and alachlor determined in the extracts by gas-liquid chromatography with electrolytic conductivity detection in the nitrogen mode or by capillary column gas chromatography with a nitrogen-phosphorus detector (7). The detection limit is about 0.1 µg/litre.

15.2.3. Environmental levels and human exposure

Water

Alachlor was detected in the surface water and groundwater of 10 states of the USA between 1979 and 1987 (3). In two recent surveys in the USA, alachlor was detected in one of 750 and in 38 of 1430 private wells sampled (A.J. Klein, Monsanto Agricultural Company, personal communication). A review of monitoring data showed that alachlor was present in groundwaters in the USA at levels ranging from less than 0.1 to 16.6 µg/litre (8). In Italy, in a survey carried out in 1987-88, alachlor was detected in three out of 322 drinking-water supplies at a maximum level of 1.6 µg/litre (9).

Food

Food does not appear to be a major route of exposure for the general population since residues of alachlor in food are usually below the detection limit. It is rapidly metabolized by crops after application and does not bioaccumulate (1). In tolerant plants, it is detoxified by rapid conjugation with glutathione (10).

15.2.4. Kinetics and metabolism in laboratory animals and humans

Alachlor is absorbed through the gastrointestinal tract of rats and distributed to the blood, spleen, liver, kidney, heart, and, to a lesser extent, eyes, brain, stomach, and ovaries (11). Rats, mice, and monkeys differ in the ways in which they metabolize, distribute, and excrete it (12-14). 4-Amino-3,5-diethylphenol, which is suspected to be a key metabolite from the point of view of the carcinogenicity of alachlor, has been found in much larger quantities in the urine of rats than in that of mice and monkeys. Alachlor and its metabolites in urine and faeces are excreted much slowly in rats than in mice and monkeys. Mice excrete alachlor metabolites mainly via the faeces, rats in equal proportions in the urine and faeces, and monkeys mainly via urine (15,16).

15.2.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Acute oral LD₅₀s of 930-1350 and 1100 mg/kg of body weight for rats and mice, respectively, have been reported (2).

Short-term exposure

In a 6-month feeding study, dogs were given alachlor at 0, 5, 25, 50, or 75 mg/kg of body weight per day; dose-related hepatotoxicity was seen at all dose levels (17). In a subsequent 1-year feeding study in which dogs were given alachlor at 1, 3, or 10 mg/kg of body weight per day, the NOAEL was 1 mg/kg of body weight per day (18).

Long-term exposure
A 2-year feeding study in Long-Evans rats showed alachlor to be toxic at all doses tested (14, 42, or 126 mg/kg of body weight per day). Effects observed included dose-related hepatotoxicity at all dose levels and highly significant levels of ocular lesions, identified as the uveal degeneration syndrome, in the mid- and high-dose groups (19). In another 2-year feeding study in which the same strain of rats was given alachlor at 0, 0.5, 2.5, or 15 mg/kg of body weight per day, 2.5 mg/kg of body weight per day dose was considered to be the NOAEL for uveal degeneration syndrome (20).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a three-generation study, 10 male and 20 female CD rats were fed a diet containing 0, 3, 10, or 30 mg of alachlor per kg. No effects were observed on the reproductive cycle or on postnatal development (21). After female CD rats were treated by gastric intubation with 0, 50, 150, or 400 mg of technical alachlor per kg of body weight per day from days 6 to 19 of gestation, no signs of embryotoxicity were observed at any of the doses tested (22).

Female Dutch Belted rabbits were exposed to alachlor by gavage on days 7-19 of gestation at 0, 10, 30, or 60 mg/kg of body weight per day. No signs of maternal toxicity or embryotoxicity were observed at these doses (23).

Mutagenicity and related end-points

Alachlor does not induce gene mutations in bacteria and in mammalian cells in vitro (24), but does induce chromosomal aberrations in mammalian cells in vitro (25) and is weakly active in a gene conversion test in yeast (26) and in an in vitro/vivo test of DNA repair in rat hepatocytes (27). Samples of varying purity gave contrasting results for chromosomal aberrations in in vivo tests in the rat (26,28). A broad spectrum of genetic damage was observed in plant systems (29,30). There are positive mutagenicity data for 2,6-diethylaniline, which is a known metabolite of alachlor in animals.

Carcinogenicity

Doses of 0, 14, 42, or 126 mg/kg were administered in the diet to Long-Evans rats (50 of each sex) for 2 years. This study provided clear evidence of carcinogenicity based on a statistically significant increase in the incidence of adenomas of the nasal turbinate, malignant stomach tumours, and thyroid follicular tumours in high-dose males. This conclusion is also based on the incidence of adenocarcinomas of the nasal turbinate in mid-dose males and females and the observation of submucousal hyperplasia in nasal tissues, and was supported by a repeated study of the highest dose only (126 mg/kg), in which adenomas and adenocarcinomas of the nasal cavity and malignant stomach tumours were found (31).

A second study on the same rat strain using doses of 0, 0.5, 2.5, and 15 mg/kg for 2 years also provided clear evidence of carcinogenicity. A statistically significant increase in the incidence of adenomas of the nasal turbinate was observed at the highest dose. Submucosal gland hyperplasia of the nasal turbinate was also noted. The presence of stabilizers in the technical material is unlikely to have influenced the carcinogenic response observed in the rat (20).

CD-1 mice were fed technical-grade alachlor in the diet for 18 months at doses of 0, 26, 78, or 260 mg/kg of body weight per day. Statistically significant increases in lung bronchiolar tumours at the highest dose tested were seen in female mice (32). The increase of lung tumours in male mice was not significant at any dose. In the United States, the Environmental Protection Agency has concluded that this study provides inadequate evidence of carcinogenicity (A.J. Klein, Monsanto Agricultural Company, personal communication).

15.2.6. Effects on humans
The probable oral lethal dose in humans is 0.5-5 g/kg of body weight

1 Source: Toxicology Data Bank, Bethesda, MD, National Library of Medicine.

15.2.7. Guideline value

IARC has not evaluated alachlor. On the basis of available experimental data, evidence for the genotoxicity of alachlor is considered to be equivocal. However, a metabolite of alachlor has been shown to be mutagenic. Available data from two studies in rats clearly indicate that this compound is carcinogenic, causing benign and malignant tumours of the nasal turbinate, malignant stomach tumours, and benign thyroid tumours.

In view of the data on carcinogenicity, guideline values were calculated by applying the linearized multistage model to data on the incidence of nasal tumours in rats (20). Concentrations of 200, 20, and 2 µg/litre in drinking-water are associated with excess lifetime cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$, respectively.

References


29. Singh HN, Singh HR, Vaishampayan A. Toxic and mutagenic action of the herbicide alachlor (lasso) on various strains of the nitrogen-fixing blue-green alga *Nostoc muscorum* and characterization of the herbicide-induced mutants resistant to methylanine-dl-sulfoximine. *Environmental experiments in botany*,...
1978, 19:5-12.


15.3 Aldicarb

15.3.1. General description

Identity

CAS no.: 116-06-3
Molecular formula: C₇H₁₄N₂O₂S

Aldicarb is the common name for 2-methyl-2(methylthio)propionaldehyde O-methylcarbamoyloxime.

Physicochemical properties (1-3)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapour pressure</td>
<td>13 Pa at 25 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>6 g/litre at 20 °C</td>
</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>1.359</td>
</tr>
</tbody>
</table>

Major uses

Aldicarb is a systemic carbamate insecticide used to control nematodes in soil and insects and mites on a wide variety of crops, including citrus fruits, grain, peanuts, potatoes, soy beans, sugar-beet, and tobacco.

Environmental fate

Aldicarb is oxidized by microorganisms in soil to the sulfoxide and sulfone (4); its degradation half-life ranges from a few days to more than 2 months (5, 6). Aldicarb and its degradation products are generally mobile in soil (5, 6); leaching is most extensive in soils with a low content of organic matter (5).

Aldicarb is very persistent in groundwaters, particularly those that are acidic; the half-life for degradation to nontoxic products ranges from a few weeks to as long as several years (7). The primary mode of degradation is chemical hydrolysis, although there may also be some microbial decay in shallow groundwater (8).

15.3.2. Analytical methods

Aldicarb and its degradation products in water may be determined by high-performance liquid chromatography (3). When followed by post-column derivatization to form fluorescent compounds, this method has detection limits of about 1.3, 0.8, and 0.5 µg/litre for aldicarb, the sulfoxide, and the sulfone, respectively (9). Aldicarb and its oxidation products can also be determined as their nitrile derivatives by capillary gas chromatography with a nitrogen-phosphorus detector (10).
15.3.3. Environmental levels and human exposure

Water

Aldicarb was detected in 111 of 1017 samples in surveys of private and municipal drinking-water supplies in Canada (detection limits 0.01-3.0 µg/litre); the maximum concentration was 28 µg/litre (11). Aldicarb has been detected in well-water in the USA at concentrations ranging from less than 10 to 500 µg/litre (7). Neither aldicarb nor its metabolites were detected in over 700 community groundwater drinking supplies in Florida (detection limit 2-5 µg/litre for each compound) (12). Concentrations in groundwater near potato fields to which it had been applied were detectable (≥1 µg/litre) in 31.3% of samples taken in Long Island, NY; 0.9% of samples contained aldicarb at concentrations above 100 µg/litre (13). Aldicarb sulfoxide and aldicarb sulfone residues are found in an approximately 1:1 ratio in groundwater (5,6).

Food

Aldicarb was detected in 94% of potatoes analysed in the USA in 1980 at concentrations ranging from 50 to 520 µg/kg (14). Aldicarb sulfoxide was found in 1981-1986 in seven of 6391 samples of domestic agricultural commodities at levels at or below 1.0 mg/kg (15).

Estimated total exposure and relative contribution of drinking-water

Based on maximum residue limits for aldicarb established by the Codex Alimentarius Commission (16), the theoretical maximum daily intake of aldicarb from food is about 0.09 mg/day for a 60-kg adult (1.5 µg/kg of body weight per day). The average daily intake for a male aged 25-30 years has been estimated to be 0.2 µg/kg of body weight per day, based on residues in foods in the USA (17).

Based on a concentration of aldicarb in drinking-water of 5 µg/litre and consumption of 2 litres of drinking-water per day by a 60-kg adult, the daily intake by this route can be estimated to be 10 µg (0.2 µg/kg of body weight), which is about the same as that from food.

15.3.4. Kinetics and metabolism in laboratory animals and humans

Aldicarb is rapidly absorbed from the gastrointestinal tract, the respiratory tract, and the skin. It is rapidly oxidized to aldicarb sulfoxide, which is metabolized more slowly by oxidation and hydrolysis to aldicarb sulfone. Both metabolites and the parent compound are degraded to the corresponding oximes and nitriles, which are then broken down into aldehydes, acids, and alcohols (1,18).

Elimination of aldicarb is rapid; in rats, 80% of an orally administered dose was eliminated in the urine within 24 h (19). It does not accumulate in tissues (19), but appears to cross the placental barrier (20).

Aldicarb forms a complex with acetylcholinesterase, thus inhibiting the enzyme’s action. The complex can dissociate to form aldicarb and the enzyme or break down into the oxime plus a carbamylated enzyme, which is then hydrolysed into the free enzyme and methyl carbamic acid, thus detoxifying the insecticide (18,21).

15.3.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Aldicarb is highly acutely toxic in animals; the oral LD₅₀ in rats ranges from 650 to 930 µg/kg of body weight (22), depending on the vehicle (21). The oral LD₅₀ in rats for aldicarb sulfoxide is similar to that of the parent compound, whereas the LD₅₀ for the sulfone is approximately 25 times higher (18).

Short-term exposure
A 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone was administered in drinking-water to Wistar rats (10 per sex per dose) at nominal concentrations of 0, 0.075, 0.3, 1.2, 4.8, or 19.2 mg/litre for 29 days. Mean plasma and erythrocyte cholinesterase activities were reduced by 54-77% in both males and females at 19.2 mg/litre at 8, 15, and 29 days. Although male rats exposed to 4.8 mg/litre experienced a 28% reduction in plasma cholinesterase activity at day 8 and a 25% reduction in erythrocyte cholinesterase activity at day 29, the authors considered these effects to be of questionable biological significance and determined the "no-ill-effect level" to be 4.8 mg/litre, equivalent to 0.5 mg/kg of body weight per day. Because the actual concentration in drinking-water was on average approximately 80% of the nominal concentration (1,23), the NOAEL can be considered to be 0.4 mg/kg of body weight per day.

Long-term exposure

Groups of rats (15 per sex per dose, strain unspecified) were fed diets containing concentrations of aldicarb sulfoxide equivalent to doses of 0, 0.125, 0.25, 0.5, or 1.0 mg/kg of body weight per day for 6 months. Plasma and erythrocyte cholinesterase activities were depressed in males consuming 0.25 mg/kg of body weight per day and above and in females consuming 0.5 mg/kg of body weight per day and above. No cholinesterase inhibition was observed in rats allowed to recover for 1 day before sacrifice. The NOAEL for cholinesterase inhibition was considered to be 0.125 mg/kg of body weight per day (1,24).

In a 2-year study, groups of rats (20 per sex per dose) were fed diets containing aldicarb (0.3 mg/kg of body weight per day), aldicarb sulfoxide (0.3 or 0.6 mg/kg of body weight per day), aldicarb sulfone (0.6 or 2.4 mg/kg of body weight per day), or a 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone (0.6 or 1.2 mg/kg of body weight per day). Plasma cholinesterase activity and body weight gain were depressed in males consuming 1.2 mg/kg of body weight per day of the aldicarb sulfoxide/sulfone mixture. Mortality was increased in male and female rats consuming 0.6 mg of aldicarb sulfoxide per kg of body weight per day. The authors considered the NOAELs to be 0.3 mg/kg of body weight per day for aldicarb and aldicarb sulfoxide, 2.4 mg/kg of body weight per day for aldicarb sulfone, and 0.6 mg/kg of body weight per day for the 1:1 mixture of aldicarb sulfoxide and sulfone (25).

No adverse effects were observed in two 2-year studies in which rats (26) and beagle dogs (27) were fed aldicarb in the diet at concentrations ranging from 0 to 0.1 mg/kg of body weight per day.

Reproductive toxicity, embryotoxicity, and teratogenicity

No significant effects on fertility, gestation, viability of offspring, lactation, mean weights, or histological features in litters were observed in a three-generation reproduction study in CFE rats in which aldicarb was administered in the diet at doses of 0.05 or 0.1 mg/kg of body weight per day (28). In a three-generation study in Harlan-Wistar albino rats, there was a significant difference in the body weight of second-generation pups at 0.7 mg/kg of body weight per day (29), although no adverse effects on reproduction were observed when aldicarb sulfone was administered in the diet at doses of up to 9.6 mg/kg of body weight per day (30).

Single doses of 0.001, 0.01, or 0.1 mg of aldicarb per kg of body weight per day administered by gastric intubation to pregnant Sprague-Dawley rats on day 18 of gestation caused a significant inhibition of brain acetylcholinesterase activity, which was greater in fetal than in maternal tissues (20,31).

No significant differences in fetal malformations or developmental variations were observed in the offspring of pregnant Dutch Belted rabbits administered daily aldicarb doses of 0, 0.1, 0.25, or 0.50 mg/kg of body weight per day via gavage on days 7-27 of gestation (32). Similarly, teratogenic effects were not observed in a study in which pregnant CD rats were given up to 0.5 mg/kg of body weight per day orally for 10 days during gestation (1,33).

Mutagenicity and related end-points
Most in vivo and in vitro assays of aldicarb for mutagenicity have been negative (34,35), although increases in both chromosomal aberrations in bone marrow cells (36) and sister chromatid exchange in cultured human lymphocytes (1,37) have been observed.

**Carcinogenicity**

No significant increases in the incidence of tumours of any type were reported in studies in rats (0-0.3 mg/kg of body weight per day) and mice (0-0.7 mg/kg of body weight per day) fed aldicarb in the diet for periods ranging from 18 months to 2 years (25,26,38,39).

15.3.6. Effects on humans

Clinical symptoms of aldicarb intoxication include dizziness, weakness, diarrhoea, nausea, vomiting, abdominal pain, excessive perspiration, blurred vision, headache, muscular convulsions, temporary paralysis of the extremities, and dyspnoea. Recovery is rapid, usually within 6 h (21).

Aldicarb is one of the most acutely toxic pesticides. Poisoning has resulted from ingestion of contaminated cucumbers at a dose ranging from 0.006 to 0.25 mg/kg of body weight (40) and contaminated melons at a dose as low as 0.0021 mg/kg of body weight (41).

Groups of four adult male volunteers ingested single doses of aqueous aldicarb of 0.025, 0.05, or 0.1 mg/kg of body weight. Cholinergic symptoms were observed at 0.1 mg/kg of body weight. A dose-related depression of acetylcholinesterase activity (47-73%), predominantly in the first 2 h following exposure, was observed in all subjects. It should be noted, however, that acetylcholinesterase levels in individuals varied considerably between 18 h and 1 h before dosing (42). In a study in which two volunteers ingested doses of aqueous aldicarb of 0.05 or 0.26 mg/kg of body weight, clinical signs of intoxication were observed only in the subject receiving 0.26 mg/kg of body weight (43).

The effects of chronic ingestion of aldicarb on human immune function were investigated in two limited cross-sectional epidemiological studies of women (1,44,45). In the first study, an association was found between the consumption of aldicarb in drinking-water (1-61 µg/litre) and abnormalities in various subsets of T-cell populations in women with otherwise intact immune systems (44). However, the study had several limitations, including the limited size of the exposed group, the failure to calculate aldicarb dose on a body weight basis, and the failure to match exposed and control groups with respect to water supply. In a follow-up study (45), which suffered from many of the same limitations as the first, the authors concluded that changes in the cellular distribution of immune system parameters occurred in women exposed to aldicarb in their drinking-water. The findings of these studies suggest that further research on the effects of aldicarb on the immune system is warranted.

A significant association between the age-adjusted rates for all neurological syndromes and increasing aldicarb concentration was found in a study on the relationship between levels of aldicarb in drinking-water and delayed neuropathy (46). Information on somewhat subjective symptoms was obtained from individuals by self-administered questionnaire; no clinical examinations were conducted. It was not reported whether the subjects were classified blindly on the basis of the results of the questionnaire or whether the respondents were aware of their exposure status.

No relationship between aldicarb concentrations in drinking-water and food consumption or other reported symptoms or diagnosed illnesses was found in a survey of 1035 residents of 462 households in Long Island, NY (47).

15.3.7. Guideline value

IARC has concluded that aldicarb is not classifiable as to its carcinogenicity (Group 3) (48). The only
consistently observed toxic effect with both long-term and single-dose administration of aldicarb in studies conducted to date is the rapidly reversible inhibition of acetylcholinesterase activity. The toxic effects of aldicarb appear to be dependent both on the method (i.e. single or repeated dosing) and the means of administration (e.g. by gavage, in the diet or in drinking-water), possibly because of reduced bioavailability of the compound or the bolus effect of certain forms of administration. The studies considered most appropriate for the derivation of the guideline, therefore, are those in which aldicarb was administered in the diet or drinking-water.

In 1992, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) recommended an ADI of 0.003 mg/kg of body weight, based on a single oral dose study in human volunteers with a NOAEL of 0.025 mg/kg of body weight per day and an uncertainty factor of 10 (49).

For the purposes of deriving a guideline value for drinking-water, the TDI is derived from a NOAEL of 0.4 mg/kg of body weight per day for acetylcholinesterase inhibition found in a 29-day study in rats given drinking-water containing a 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone (1,23). This study is considered to be the most relevant to the derivation of a drinking-water guideline because the rats were given water containing the two aldicarb metabolites in a ratio similar to that normally found in drinking-water. Based on an uncertainty factor of 100 (for inter- and intraspecies variation), the TDI is 4 µg/kg of body weight. No allowance was made for the short duration of the study in view of the extremely sensitive and rapidly reversible biological end-point used. The guideline value is 10 µg/litre (rounded figure), assuming an allocation of 10% of the TDI to drinking-water.

References


47. Whitlock NH, Schuman SH, Loadholt CB. *Executive summary and epidemiologic survey of potential acute health effects of aldicarb in drinking water-Suffolk County, N.Y.* Charleston, South Carolina Pesticide Hazard Assessment Program Center, Medical University of South Carolina, 1982 (prepared for the Health Effects Branch, Hazard Evaluation Division, Office of Pesticide Programs, US Environmental Protection Agency).


15.4 Aldrin and dieldrin

15.4.1. General description

**Identity**

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS no.</th>
<th>Molecular formula</th>
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<tbody>
<tr>
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<td>309-00-2</td>
<td>C_{12}H_8Cl_6</td>
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<tr>
<td>Dieldrin</td>
<td>60-57-1</td>
<td>C_{12}H_8Cl_6O</td>
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</table>

The IUPAC name for aldrin is (1R,4S,4aS,5S,5R,6R,7S,8aR)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene (HHDN). Aldrin is most commonly used to mean HHDN with a purity greater than 95%, except in Denmark and the countries of the former Soviet Union, where it is the name given to pure HHDN. Impurities include octachlorocyclopentene, hexachlorobutadiene, toluene, and polymerization products (1).

The IUPAC name for dieldrin is (1R,4S,4aS,5R,6R,7S,8aS,8aR)-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene (HEOD). Dieldrin is most commonly used to mean HEOD with a purity greater than 85%, except in Denmark and the countries of the former Soviet Union, where it is the name given to pure HEOD. Impurities include other polychloroepoxyoctahydrodimethanonaphthalenes and endrin (1).

**Physicochemical properties (1,2)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Technical aldrin (95% pure)</th>
<th>Technical dieldrin</th>
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<tr>
<td>Melting point (°C)</td>
<td>49-60</td>
<td>175-176</td>
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</table>
Density at 20 °C (g/cm³) 1.54 1.62
Water solubility at 20 °C (µg/litre) 27 186
Log octanol-water partition coefficient 3.0 4.6
Vapour pressure at 20 °C (Pa) $8.6 \times 10^{-3}$ $0.4 \times 10^{-3}$

**Organoleptic properties**

Odour threshold values of 17 and 41 µg/litre have been reported for aldrin and dieldrin, respectively (3,4).

**Major uses**

Aldrin and dieldrin are highly effective insecticides for soil-dwelling pests and for the protection of wooden structures against termites and wood borers. Dieldrin has also been used against insects of public health importance (1). Although the use of aldrin and dieldrin has been severely restricted or banned in many parts of the world since the early 1970s, they are still used in termite control in some countries (5).

**Environmental fate**

In soil, aldrin is removed by oxidation to dieldrin and evaporation. In temperate climates, only 75% is oxidized within a year after application. The further disappearance of dieldrin is very slow under these conditions; the half-life is approximately 5 years. Under tropical conditions, both oxidation and further disappearance of dieldrin are rapid, 90% disappearing within 1 month, primarily by volatilization (1).

**15.4.2. Analytical methods**

Aldrin and dieldrin are determined by extraction with pentane followed by gas chromatography with electron-capture detection. The detection limits in tap-water and river water are about 0.001 µg/litre for aldrin and 0.002 µg/litre for dieldrin.

**15.4.3. Environmental levels and human exposure**

**Air**

Dieldrin has been detected at very low concentrations in ambient air, on dust particles, and in rainwater. In nonagricultural areas, concentrations of 0.06-1.6 ng/m³ have been reported; in agricultural areas, mean levels are in the range 1-2 ng/m³, with a maximum of about 40 ng/m³ (1).

Concentrations found in the air of houses treated for termites are much higher (40-7000 ng/m³). The presence of aldrin/dieldrin-treated wood in houses results in indoor air concentrations of 10-500 ng/m³ (1).

**Water**

The concentrations of aldrin and dieldrin in aquatic environments and drinking-water are normally less than 10 ng/litre. Higher levels are attributed to contamination from industrial effluents and soil erosion during agricultural use. River sediments may contain higher amounts (up to 1 mg/kg). These pesticides are rarely present in groundwater, as little leaching from soils occurs (1).

**Food**

Dieldrin is stored in the adipose tissue, liver, brain, and muscle of mammals, fish, birds, and other parts of the food-chain. The reduction in use since the 1970s has decreased the residues in food in many countries to well below the levels that may result in an intake of 0.1 µg/kg of body weight per day (the ADI established by the Joint FAO/WHO Meeting on Pesticide Residues) (6). The intake in 1980-82 was estimated to be 0-0.2 µg/kg of body weight per day in several countries (1).
Dieldrin has been detected in breast milk at a mean concentration of 0.5-11 µg/kg of milk in Europe and the USA. Breast-fed babies receive doses of approximately 1 µg/kg of body weight per day when mothers’ milk contains 6 µg of dieldrin per litre (1). Although concentrations in breast milk decreased from an average of 1.33 µg/kg of milk in 1982 to 0.85 µg/kg of milk in 1986 (7), higher concentrations (mean 13 µg/litre) have been found in breast milk from women whose houses were treated annually with aldrin (8).
15.4.4. Kinetics and metabolism in laboratory animals and humans

Aldrin and dieldrin are absorbed by the oral, inhalation, and dermal routes. They tend to accumulate in adipose tissue. A steady state between intake, storage, and excretion is reached following repeated dosing. Aldrin and dieldrin can be mobilized from the adipose tissue compartment, causing an increase in blood level that results in toxic manifestations. Dieldrin is metabolized in the liver and is excreted, with its metabolites, primarily in the faeces via the bile in humans and in most animals tested (mouse, rat, monkey). The major metabolite is 9-hydroxy dieldrin. Small amounts of trans-6,7-hydroxy dieldrin, dicarboxylic acids, and bridged pentachloroketone are excreted, but only in laboratory animals. The ratios between the amounts of the various metabolites produced differ for different animals (1).

15.4.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Acute oral LD₅₀s of 33-65 mg/kg of body weight have been reported for aldrin and dieldrin for mice, rats, dogs, pigs, and rabbits. The reported value for dieldrin in monkeys is 3 mg/kg of body weight (1).

Short-term exposure

Short-term studies on rodents have shown that the liver is the major target organ of aldrin and dieldrin exposure. The liver-to-body-weight ratio increases, and histopathological changes are observed, which have become known as “chlorinated hydrocarbon insecticide rodent liver.” In rats, the changes were minimal at a dose of 0.025 mg/kg of body weight per day, and this value was selected as the LOAEL (1).

Long-term exposure

Dogs seem more sensitive to aldrin and dieldrin than rats. In a 2-year study with beagle dogs receiving dieldrin in olive oil at doses of 0.005 or 0.05 mg/kg of body weight per day, female dogs given 0.05 mg/kg of body weight per day had an increased liver-to-body-weight ratio. The NOAEL was estimated to be 0.005 mg/kg of body weight per day (1).

Reproductive toxicity, embryotoxicity, and teratogenicity

The results of a number of reproductive studies suggest that dieldrin at levels of 2 mg/kg in the rat diet and 3 mg/kg in the mouse diet has no effects on reproduction. At these levels, however, there may be biochemical and histopathological effects.

In a limited study with dogs fed aldrin or dieldrin, pup survival was generally lower. No effects were observed in dogs receiving 0.2 mg of dieldrin per kg in the diet (1).

Mutagenicity and related end-points

The majority of studies on aldrin and dieldrin have not shown them to be mutagenic. In one study in which dieldrin was mutagenic in two out of three strains of Salmonella typhimurium, a dose-response relationship was not demonstrated (1).

Carcinogenicity

A number of long-term studies have shown aldrin and dieldrin to produce benign and malignant tumours of the liver in various strains of mice but not in other species. This indicates that the effect of aldrin/dieldrin on the mouse liver is species-specific. Aldrin and dieldrin have also been tested for carcinogenicity by the oral route in hamsters, dogs, and monkeys (1). After assessing much of the available data, IARC concluded that the evidence for the carcinogenicity to animals for both aldrin and dieldrin is limited, and
classified both chemicals in Group 3 (9).

15.4.6. Effects on humans

Both aldrin and dieldrin are highly toxic to humans, the target organs being the central nervous system and the liver. Severe cases of both accidental and occupational poisoning and a number of fatalities have been reported. The lethal dose of dieldrin is estimated to be approximately 10 mg/kg of body weight per day. The majority of those poisoned by aldrin or dieldrin recover, and irreversible effects have not been reported.

Male volunteers exposed to dieldrin doses of 0-3 µg/kg of body weight per day for 18 months showed no effects on health. The concentration of dieldrin in blood and adipose tissue was found to be proportional to the daily intake (1).

Effects on occupationally exposed workers have been studied in two epidemiological mortality studies. In one study (232 subjects), no indication of specific carcinogenic activity was found. In another study (1040 subjects), the mortality due to malignant neoplasms was lower than expected. There was a slight excess of cancers of the oesophagus, rectum, and liver, based on very small numbers. The only disease showing higher mortality rates than expected was nonmalignant respiratory system disease, specifically pneumonia (1).

Chromosome studies have been carried out on human peripheral lymphocytes from agricultural workers and workers engaged in the control of Chagas disease with at least 10 years of exposure to dieldrin. There were no differences between the control and exposure groups in structural chromosomal aberrations and sister chromatid exchange (1).

15.4.7. Guideline value

As already mentioned, IARC has classified aldrin and dieldrin in Group 3 (9). All the available information on aldrin and dieldrin taken together, including studies on humans, supports the view that these chemicals make very little contribution, if any, to the incidence of cancer in humans. Therefore, a TDI approach can be used to calculate a guideline value.

In 1977 JMPR recommended an ADI of 0.1 µg/kg of body weight (combined total for aldrin and dieldrin). This was based on NOAELs of 1 mg/kg of diet in the dog and 0.5 mg/kg of diet in the rat, which are equivalent to 0.025 mg/kg of body weight per day in both species. JMPR applied an uncertainty factor of 250 based on concern about carcinogenicity observed in mice (6).

This ADI is reaffirmed. Although levels of aldrin and dieldrin in food have been decreasing, dieldrin is highly persistent and bioaccumulates. There is also the potential for exposure in the atmosphere of houses where it is being used for termite control. The guideline value is therefore based on an allocation of 1% of the ADI to drinking-water, giving a value of 0.03 µg/litre.

References


15.5 Atrazine

15.5.1. General description

*Identity*

CAS no.: 1912-24-9  
Molecular formula: C₈H₁₄ClN₅

The IUPAC name for atrazine is 6-chloro-N-ethyl-N'-isopropyl-1,3,5-triazine-2,4-diamine or 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine (1). Most commercial atrazine products are about 95% pure. Common impurities include sodium chloride and other symmetric triazines, such as simazine and propazine.

*Physicochemical properties (1-3)*

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<td>Vapour pressure</td>
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</table>

*Major uses*

Atrazine is used as a selective pre- and post-emergence herbicide for the control of weeds in asparagus, maize, sorghum, sugar-cane, and pineapple. It is also used in forestry and for non-selective weed control on non-crop areas (1). Several countries have restricted its use.

*Environmental fate*

Atrazine can be degraded in surface water by photolysis and microorganisms via N-dealkylation and hydrolysis of the chloro substituent; the corresponding half-lives are greater than 100 days at 20 °C. Hydrolysis and microbial degradation also take place in soil, depending mainly on temperature, moisture, and pH. Half-lives of 20-50 days at 20-25 °C have been found under laboratory conditions, increasing at lower temperatures (4). These are similar to the half-lives found under natural conditions, but longer half-lives have been seen under special conditions (5). Degradation rates normally decrease with increasing
depth, and atrazine can be fairly stable in groundwater (6).

Atrazine’s degradation products in soil include 2-chloro-4-amino-6-isopropylamino-1,3,5-triazine, 2-chloro-4-ethylamino-6-amino-1,3,5-triazine, 2-chloro-4-amino-6-amino-1,3,5-triazine, 2-hydroxy-4-ethylamino-6-isopropylamino-1,3,5-triazine, and 2-hydroxy-4-amino-6-isopropylamino-1,3,5-triazine (the main metabolite) (7). Unsubstituted amino metabolites and triazine are formed later and may be mineralized completely. Atrazine and its dealkylated metabolites are moderately to very mobile in sandy, silt, and clay soils (8). Hydroxytriazines, however, are of low mobility (9) and persist for long periods in the soil (10).

15.5.2. Analytical methods

Atrazine is determined by extraction with pentane followed by gas chromatography with nitrogen-phosphorus detection. The detection limit in tapwater and river water is about 0.1 µg/litre.

15.5.3. Environmental levels and human exposure

Air

Evaporation tests in fields treated with atrazine have shown a loss of about 0.2% of the dose per day. It is found in precipitation just after spraying (11) and may then also be expected to be found in air.

Water

In many countries, after application in agricultural areas, atrazine has been found in groundwater at levels of 0.01-6 µg/litre. It has also been detected in drinking-water in several countries at levels of 0.01-5 µg/litre (11,12).

Food

Hydroxy metabolites of atrazine have been found in plants grown in soil treated with it (10), but atrazine itself has not been found on crops. When sprayed on maize, it is quickly transformed by the plant into its hydroxy metabolites (13).

15.5.4. Kinetics and metabolism in laboratory animals and humans

Atrazine appears to be readily absorbed from the gastrointestinal tract. In a study of rats given a single dose by gavage, at least 80% of the dose was absorbed. Within 3 days, 66% of the dose was excreted in the urine, 14% was retained in tissues, mainly the blood cells, and only 0.1% was found in the expired air (14). Doses given orally are retained mainly in erythrocytes, liver, spleen, and kidney. Most of the metabolites found in soil can also be found as degradation products in rats, with 2-chloro-4,6-diamino-1,3,5-triazine being the major compound present in urine (15). Absorption through skin is limited, amounting to less than 2% after a 10-h exposure (16).

15.5.5. Effects in laboratory animals and in vitro test systems

Acute exposure

When technical atrazine (97% active ingredient) was administered to very young rats (<7 weeks), LD<sub>90</sub>s of 1900-2300 mg/kg of body weight were found, whereas LD<sub>90</sub>s in the range 670-740 mg/kg of body weight were found for 3-month-old rats (17). LD<sub>50</sub>s of 1750-4000 mg/kg of body weight were established in mice (18).

Atrazine causes moderate irritation to rabbit skin but is not appreciably irritating to the rabbit eye. It causes dermal sensitization in the guinea-pig. The dermal LD<sub>50</sub> was reported to be higher than 3100 mg/kg of
Short-term exposure

A 2-week study on female rats on oral toxicity and hormonal effects showed that 100 mg/kg of body weight per day influenced the serum concentration of estrogen, luteinizing hormone, prolactin, and progesterone. These effects may be important in the development of breast cancer in rats (20).

Long-term exposure

In a 1-year oral study on beagle dogs with technical atrazine (97% active ingredient) at doses of 0, 0.5, 5, or 34 mg/kg of body weight per day, the heart was the main target organ. Dogs given 34 mg/kg of body weight per day showed ECG alterations and clinical signs referable to cardiac toxicity after only 17 weeks. Treatment-related changes in haematological values were also reported in males of this group. Slight decreases in total serum protein and albumin were reported for males at 34 mg/kg of body weight per day. The NOAEL in this study was 5 mg/kg of body weight per day (21).

Technical atrazine (98.9% active ingredient) was fed to Sprague-Dawley rats for 2 years at 0, 10, 70, 500, or 1000 mg/kg in the diet. At 500 and 1000 mg/kg, there was a significant decrease in mean body weights of both sexes and decreased food consumption. At 1000 mg/kg, females were found to have a consistent reduction in red blood cell count, haemoglobin and haematocrit, and glucose levels were depressed in both females and males during the first 12 months. The NOAEL in this study was 70 mg/kg (equivalent to 3.5 mg/kg of body weight per day) based on non-neoplastic effects as well as reduced body weight and food consumption (22).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a two-generation rat study utilizing technical atrazine (97% active ingredient) in doses of 0, 0.5, 2.5, or 25 mg/kg of body weight per day, pup weights in the second generation at the two highest doses were statistically significantly lower than those of the control group. Both parental animals had significant decreases in body weight, body weight gain, and food consumption at 25 mg/kg of body weight per day. In addition, a statistically significant increase in relative testis weight was seen in both generations at this dose level. Thus, the reproductive NOAEL was 0.5 mg/kg of body weight per day, and the parental NOAEL 2.5 mg/kg of body weight per day (23).

No teratogenic response was found in New Zealand white rabbits that received atrazine by gavage on days 7-19 of gestation at dose levels of 1, 5, or 75 mg/kg of body weight per day. Maternal toxicity, in the form of decreased body weight gain and food consumption, was seen in the mid- and high-dose groups. Fetotoxicity was demonstrated only at 75 mg/kg of body weight per day by an increased resorption rate, reduced fetal weights, and delay of ossification. The embryotoxic NOAEL appears to be 5 mg/kg of body weight per day, and the maternal NOAEL is 1 mg/kg of body weight per day (24).

Mutagenicity and related end-points

Atrazine has been tested in several systems, but there is no convincing evidence that it has any significant genotoxic action. However, deficiencies exist with respect to certain of the tests performed, and some evidence of genotoxic effects in vivo needs confirmation (25-28).

Carcinogenicity

In the study in which technical atrazine (98.9% active ingredient) was fed to Sprague-Dawley rats for 2 years at 0, 10, 70, 500, or 1000 mg/kg in the diet, a significant increase in the incidence of mammary tumours in females was seen at the three highest doses (22). The doses in the middle of the range (70 and 500 mg/kg) showed 95% significance for the occurrence of adenocarcinomas and carcinosarcomas,
suggesting that atrazine interferes with hormonal regulation in male rats. The effect of atrazine on rat hormones confirms this hypothesis (20). The NOAEL in this study was 10 mg/kg, equivalent to 0.5 mg/kg of body weight per day. Studies on mice have not shown any signs of tumours (29).

15.5.6. Effects on humans

In an epidemiological study in northern Italy, an increased relative risk of ovarian neoplasia was found among women exposed to triazine herbicides (30). An 80% formulation of atrazine did not cause skin sensitization on repeated application to humans.

15.5.7. Guideline value

The weight of evidence from a wide variety of genotoxicity assays indicates that atrazine is not genotoxic. There is some evidence that it can induce mammary tumours in rats as a result of hormonal changes, but it is highly probable that the mechanism for this process is non-genotoxic. No significant increase in neoplasia has been observed in mice. IARC has concluded that there is inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of atrazine (Group 2B) (31).

A TDI approach can therefore be used to calculate a guideline value. Based on a NOAEL of 0.5 mg/kg of body weight per day in a carcinogenicity study in the rat (22) and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 to reflect potential neoplasia), a TDI of 0.5 µg/kg of body weight can be calculated. With an allocation of 10% of the TDI to drinking-water, the guideline value is 2 µg/litre (rounded figure).

References

10. Kahn SU, Saidak WJ. Residues of atrazine and its metabolites after prolonged usage. Weed research,


27. Adler ID. A review of the coordinated research effort on the comparison of test systems for the detection of mutagenic effects, sponsored by the EEC. *Mutation research*, 1980, 74:77-93.


15.6 Bentazone

15.6.1 General description

**Identity**

CAS no.: 50 723-80.3  
Molecular formula: C₁₀H₁₂N₂O₃S  

The IUPAC name for bentazone is 3-isopropyl-(1H)-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide. Technical bentazone is 92-96% pure. Its main impurities are N-isopropylsulfamoyl anthranilic acid (reactant; 2.4%), sodium chloride (raw material; 1.0%), and anthranilic acid (reactant; 0.6%). Some 50 other compounds have been found as impurities at very low concentrations (1).

**Physicochemical properties (1-3)**

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</tr>
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<td>Vapour pressure</td>
<td>0.46 × 10⁻³ Pa at 20 °C</td>
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</tbody>
</table>

**Major uses**

Bentazone is a contact herbicide used in winter and spring cereals, maize, peas, rice, and soy beans. It is absorbed by the leaves and has a short herbicidal effect (2).

**Environmental fate**

The mechanism for degradation in soil is not known. The metabolite 2-amino-N-isopropyl benzamide (AIBA) has been found; two others, 6- and 8-hydroxy bentazone, may occur but are not extractable from soils after application and may be incorporated in the humic fraction. In a sandy soil assay, 80% of radioactively labelled bentazone was still present in the soil a year after application. The half-life of bentazone under optimal conditions is 1.5-15 weeks, depending on soil type. At temperatures below 10 °C, the half-life is longer than 20 weeks. In lysimeter and laboratory assays of mobility, 20-50% of bentazone and AIBA appears in the eluate (1).

15.6.2 Analytical methods

Bentazone may be determined by extraction with dichloromethane followed by gas chromatography with electron-capture detection. The detection limit in tap-water and river water is about 0.05 µg/litre (1).
15.6.3 Environmental levels and human exposure

**Air**

Bentazone is unlikely to occur in air owing to its low vapour pressure.

**Water**

Bentazone can be detected in groundwaters in cultivated areas where it is used. Surface waters can be polluted by effluents from production plants, drainage waters, and actual use in the water (rice fields). Concentrations range from <0.1 to 6 µg/litre in groundwater and from <0.1 to 2 µg/litre in surface water (4).

**Food**

Bentazone may be present in crayfish farmed in rice fields where it is sprayed (3).

15.6.4 Kinetics and metabolism in laboratory animals and humans

In rats, 14C-labelled bentazone was rapidly absorbed from the gastrointestinal tract and distributed via the bloodstream to various organs and tissues. Liver and kidneys exhibited the highest activity, but no penetration across the blood - brain barrier was observed. Of the dose administered, 90% was excreted in the urine within 24 h as unchanged bentazone. Little was recovered in the faeces (1%), and even less detected in exhaled air (<0.02%) (5). More than 80% of a single dose of bentazone administered to a rabbit in the feed was excreted in the urine un-metabolized. Two unidentified metabolites, accounting for about 3% of the dose, were detected, together with small quantities of 6- and 8-hydroxy bentazone (6, 7).

15.6.5 Effects on laboratory animals and in vitro test systems

**Acute exposure**

The acute toxicity of bentazone appears to be moderate to low. For rats, the LD50 for oral intake in carboxymethylcellulose gel was 1220 mg/kg of body weight, and for dermal exposure in water, greater than 2500 mg/litre. Poor muscle coordination, tremor, and breathing difficulties were noted, but no exposure-related pathological changes were discovered on necropsy (8, 9).

**Short-term exposure**

Beagle dogs were given technical bentazone at 0, 2.5, 7.5, 25, or 75 mg/kg of body weight per day for 13 weeks (10). The highest dose level produced weight loss, reduced haemoglobin, and fatty degeneration of liver and heart muscle. One-third of males and two-thirds of females died. Effects at lower dose levels were much less marked or absent. Prostatitis was observed in all males at 75 mg/kg of body weight per day and in one male at 25 and another at 7.5 mg/kg of body weight per day. This suggests a compound-related dose-dependent effect, with 2.5 mg/kg of body weight per day as the NOAEL (11). Others have suggested that 7.5 mg/kg of body weight per day is the NOAEL (12).

**Long-term exposure**

In a 2-year study, rats were fed bentazone in the diet at 10, 40, or 200 mg/kg of body weight per day. Decreased mean body weight gain, increased absolute and relative kidney weights, increased water consumption, and changes in urine and blood data were apparent in animals of both sexes at the highest dose level. In addition, males had depressed food consumption and an equivocal increase in eye lesions and cataracts. Less severe effects were seen in the group receiving 40 mg/kg of body weight per day, and no compound-related effects were observed at 10 mg/kg of body weight per day (13).
In a 52-week feeding study carried out in dogs at dose levels of 0, 100, 400, and 1600 mg/kg, the NOAEL was 400 mg/kg (13.1 mg/kg of body weight per day). At the highest dose, various clinical signs were observed in males, an increase in prothrombin time and in partial thromboplastin time was observed in both sexes, and two dogs showed reduced spermiogenesis (14).

In a long-term toxicity/carcinogenicity study in which mice were given bentazone at concentrations of 0, 100, 400, or 2000 mg/kg in the diet, the NOAEL was 100 mg/kg, equal to 12 mg/kg of body weight per day, based on increases in prothrombin time and changes in pituitary weights in males (15).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Pregnant Sprague-Dawley rats were given technical bentazone by gavage at doses of 22.2, 66.7, or 200 mg/kg of body weight per day on days 6 - 15 after conception. At 200 mg/kg of body weight per day, a dose level not associated with maternal toxicity, signs of fetotoxicity and teratogenicity were observed, such as increased late resorptions, fetuses with thickened and/or shortened extremities, runting, and anasarca. The NOAELs for fetuses and dams were 66.7 and 200 mg/kg of body weight per day, respectively (16).

Pregnant Wistar rats were fed bentazone at 40, 100, or 250 mg/kg of body weight per day on days 6-15 after conception. At 250 mg/kg of body weight per day, the dams showed significantly decreased food intake but no weight decrease. Signs of fetotoxicity, such as increased resorption, smaller litter sizes, and lower mean pup weight, were also noticed. The NOAEL for both fetuses and dams was 100 mg/kg of body weight per day (17).

In a two-generation rat study at dose levels of 0, 200, 800, or 3200 mg/kg of feed, no reproductive or teratogenic effects were observed. The NOAELs for reduced body weight were 800 mg/kg (50 mg/kg of body weight per day) in parental animals and 200 mg/kg (15 mg/kg of body weight per day) in pups (18).

In a study in which pregnant Chinchilla rabbits were given 75, 150, or 375 mg of bentazone per kg of body weight per day by gavage on days 6-18 of gestation, maternal toxicity was observed at the highest dose level. There were no indications of teratogenicity or effects on fetal or embryonic development at any dose level. The NOAEL was 150 mg/kg of body weight per day (19).

**Mutagenicity and related end-points**

Mutagenicity tests, Ames tests, and cytogenetic tests gave negative results, except for a mouse liver cell assay and a point mutation test carried out on CHO cells, in which bentazone gave a weak mutagenic response (20).

**Carcinogenicity**

No carcinogenic effects have been observed in the different studies carried out.

**15.6.6 Effects on humans**

No cases of human poisoning have been reported following bentazone exposure.

**15.6.7 Guideline value**

Long-term studies conducted in rats and mice have not indicated a carcinogenic potential, and a variety of in vitro and in vivo assays have indicated that bentazone is not genotoxic. The guideline value is therefore derived using a TDI approach.
JMPR evaluated bentazon in 1991 (20) and established an ADI of 0.1 mg/kg of body weight by applying an uncertainty factor of 100 to a NOAEL of 10 mg/kg of body weight per day, based on haematological effects at higher doses, derived from a 2-year dietary study in rats (13) and supported by NOAELs in dogs and mice (14, 15). To allow for uncertainties regarding dietary exposure, 1% of the ADI was allocated to drinking-water, resulting in a guideline value of 30 µg/litre.

References


10. Leuschner F et al. Thirteen week toxicity of 3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide to beagles when administered with the food. Hamburg, Pharmacology and Toxicology Laboratory, 1970 (unpublished report submitted to WHO by BASF, Limburgerhof, Germany).


15. Takehara K et al. *Studies on the 24-month chronic toxicity of bentazone reg. no. 51,929 (ZNT No. 81/273) in mice.* Nippon Institute for Biological Sciences and the Institute of Environmental Toxicology, 1985 (unpublished report submitted to WHO by BASF, Limburgerhof, Germany).


15.7 Carbofuran

15.7.1 General description

*Identity*

CAS no.: 1563-66-2  
Molecular formula: C_{12}H_{15}NO_3

Carbofuran is the common name for 2,3-dihydro-2,2-dimethylbenzofuran-7-yl-methylcarbamate.

*Physicochemical properties* (1, 2)

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</table>

*Major uses*

Carbofuran is a systemic acaricide, insecticide, and nematocide. It is used mainly on alfalfa, sugar-beet, cereals, citrus fruit, coffee, cotton, grapes, fruit trees, maize, potatoes, rice, soybeans, sugar-cane, tobacco, and vegetables (2).

*Environmental fate*

Carbofuran can dissipate from water by direct photolysis and photo-oxidation. In soil, photodecomposition is not an important degradation pathway. Volatilization from soil and water is not expected to be significant.¹
Carbofuran undergoes chemical and microbial degradation mainly through hydrolysis and hydroxylation (3, 4). Repeated applications do not result in an accumulation of residues. It does not bind to soil or sediments and has been shown to migrate extensively in soil (1). Its half-life in soil has been reported to be 1-37 weeks (5).

15.7.2 Analytical methods

Carbofuran is determined by a high-performance liquid chromatographic procedure used for the determination of N-methylcarbamoyloximes and N-methyl-carbamates in drinking-water. The detection limit has been estimated to be approximately 0.9 µg/litre (6).

15.7.3 Environmental levels and human exposure

Air

In a study designed to evaluate human exposures to carbofuran following aerial applications, it was estimated that maximum inhaled doses were in the range 0.7-2.0 mg/day (7).

Water

In the USA, carbofuran has been detected in the groundwater of seven states (8), and in 30% of 5100 groundwater samples examined (9). In a field study, it was found in groundwater 12-16 months after application to potato and corn crops on sandy soil; maximum concentrations were 10 and 30 µg/litre, respectively (9). Typical levels of 1-5 µg/litre have been reported for groundwaters in areas with sandy soils (5).

Food

Monitoring of carbofuran residues in or on foods has revealed only the occasional occurrence of low levels of the parent compound and its metabolites (10). There is no evidence for bioaccumulation or biomagnification in fish (11).

15.7.4 Kinetics and metabolism in laboratory animals and humans

Carbofuran administered to female mice by gavage was rapidly absorbed (12). Metabolism appears to involve hydroxylation and/or oxidation reactions that result in the formation of carbofuran phenols, 3-hydroxycarbofuran, 3-hydroxycarbofuran-7-phenol, 3-ketofuran, and 3-ketofuran-7-phenol. Hydrolysis is a significant pathway for carbofuran metabolism in mammals (13).

Elimination of carbofuran is rapid in rats; approximately 72% of a single orally administered dose was excreted in the urine within 24 h, and 92% after 120 h, while total faecal excretion was about 3% (13). Some pulmonary excretion has been found in mice. After 60 min, 6% and 24% of an orally administered dose were recovered as exhaled carbon dioxide and in urine, respectively (14).

15.7.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Oral LD₅₀S have been reported to be 6-34 mg/kg of body weight for the rat (15), 2.0 mg/kg of body weight for the mouse (16), and 15-19 mg/kg of body weight for the dog (15). Acute toxicity effects, including death, resulting from exposure to carbofuran are attributed to rapid inhibition of acetylcholinesterase
activity (16).

**Short-term exposure**

In a 1-year feeding study in beagle dogs exposed to carbofuran at doses of 0, 0.25, 0.5, or 12.5 mg/kg of body weight per day, no biologically significant adverse effects on various biochemical, haematological, or clinical parameters were reported at 0.25 or 0.5 mg/kg of body weight per day. At 12.5 mg/kg of body weight per day, marked depression of plasma and erythrocyte cholinesterase levels was observed in both sexes, as well as testicular degeneration and some aspermia in males, and uterine hyperplasia and hydrometria in females. The NOAEL for dogs was 0.5 mg/kg of body weight per day, based on this study (17).

**Long-term exposure**

In a 2-year study, rats were fed carbofuran in the diet at 0, 0.5, 1, or 5 mg/kg of body weight per day. At the highest dose, slight decreases in mean body weight were observed in males; there was also inhibition of plasma, red blood cells, and brain cholinesterase levels in both sexes. No adverse effects on body weight, food consumption, behaviour, ophthalmology, haematology, biochemistry, urinalysis, or histopathology were observed at the two lower doses. The NOAEL for this study was 1 mg/kg of body weight per day (18).

In a similar 2-year study in which mice were fed carbofuran in the diet at 3, 19, or 75 mg/kg of body weight per day, those receiving the highest dose showed a temporary decrease in body weight. At the two highest doses, a reduction in brain cholinesterase levels was observed. No adverse effects on food consumption, behaviour, haematology, biochemistry, urinalysis, or histopathology were observed at the lowest dose. This study supports a NOAEL of 3 mg/kg of body weight per day (19).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

In beagle dogs fed carbofuran for 1 year at 0.25, 0.5, or 12.5 mg/kg of body weight per day, aspermia in males was observed at the two highest doses. The highest dose resulted in testicular degeneration in males and uterine hyperplasia and hydrometria in females (17).

In a three-generation study in which rats were fed carbofuran at 1 or 5 mg/kg of body weight per day, no adverse effects on male or female fertility, length of gestation, litter size, or growth were observed. At the highest dose, however, the survival rate of the first litter in all three generations was slightly lower by day 4 of lactation. The NOAEL for reproductive effects was 1 mg/kg of body weight per day (20).

Dose-related inhibition of cholinesterase activity in the blood, liver, and brain of pregnant rats and their fetuses was found in a study in which carbofuran was administered orally at 0.05, 0.3, or 2.5 mg/kg of body weight on day 18 of gestation. In the high-dose group, toxic signs appeared within 5 min; 8 of 32 dams died within 30 min; and acetylcholinesterase activity was reduced in all maternal and fetal tissues sampled 1 h after dosing. At lower doses, inhibition was found in some tissues at 1 h. In this study, the LOAEL was 0.05 mg/kg of body weight for a single dose, based on the inhibition of maternal and fetal blood acetylcholinesterase and maternal liver acetylcholinesterase (21).

No teratogenic effects have been found in studies conducted on rats, mice, and rabbits (22-24). The NOAEL was 0.1 mg/kg of body weight per day in a teratology study in rats (24).

**Mutagenicity and related end-points**

Carbofuran was negative in Ames bacterial tests except for one in which it was mutagenic in *Salmonella typhimurium* strains TA98 and TA1538 with activation by rat liver homogenate (S9 fraction) (1, 25). Mutagenicity tests in other organisms were negative, except that positive results were reported with
Chinese hamster ovary V79 cells without, but not with, activation by rat liver homogenate (S9 fraction) (1, 26).

**Carcinogenicity**

No evidence of carcinogenicity was found in the 2-year dietary studies on rats and mice mentioned above (18, 19).

**15.7.6 Effects on humans**

Carbofuran was administered orally to healthy males in a controlled experiment in which there were two subjects at each dose level. The subjects were observed for 24 h after dosing. At 0.1 mg/kg of body weight, symptoms of acetylcholinesterase depression were observed, including salivation, diaphoresis, abdominal pain, drowsiness, dizziness, anxiety, and vomiting. No symptoms were observed at 0.05 mg/kg of body weight, and this dose level was defined as the NOAEL in this study (27).

Several cases of adverse effects have been reported in individuals involved in the application and formulation of carbofuran. There were mild and reversible symptoms of acetylcholinesterase depression, such as malaise, hypersalivation, and vomiting. Following more severe poisoning, symptoms included chest tightness, muscular twitching, convulsions, and coma (28).

**15.7.7 Guideline value**

IARC has not evaluated carbofuran. On the basis of the available studies, this compound appears to be neither carcinogenic nor mutagenic.

While clinical signs of acetylcholinesterase inhibition were observed in humans at a single oral dose of 0.1 mg/kg of body weight, they were absent at 0.05 mg/kg of body weight, which can therefore be regarded as a NOAEL in humans (27).

A NOAEL of 0.5 mg/kg of body weight per day was derived from a 1-year study in dogs (17). The NOAEL for systemic effects in dams in a rat teratology study was 0.1 mg/kg of body weight per day (24).

A TDI of 1.67 µg/kg of body weight was calculated by applying an uncertainty factor of 30 (10 for intraspecies variation and 3 for the steep dose-response curve) to the NOAEL of 0.05 mg/kg of body weight in humans. This TDI is supported by observations in laboratory animals, giving an adequate margin of safety for the NOAELs in rats and dogs. An allocation of 10% of the TDI to drinking-water results in the guideline value of 5 µg/litre (rounded figure).

**References**


5. Cohen SZ et al. Potential for pesticide contamination of ground water from agricultural use. In: Kruger RF, Seiber JN, eds. *Treatment and disposal of pesticide wastes*. Washington, DC, American Chemical


22. Agricultural Chemical Group. Pilot teratology study in the rat with carbofuran in the diet. Middleport,
NY, FMC Corporation, 1980 (unpublished study submitted to WHO).


15.8 Bentazone

15.8.1. General description

Identity

CAS no.: 57-47-9
Molecular formula: C_{10}H_6Cl_8

The IUPAC name for chlordane is 1,2,4,5,6,7,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene. Chlordane is a mixture of isomers, mainly cis- and trans-chlordane. Technical chlordane contains 60-75% chlordane isomers and at least 25 other compounds, including heptachlor (C_{10}H_5Cl_7), and nonachlor (C_{10}H_5Cl_9).

Physicochemical properties (1,2)

<table>
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<td>Water solubility</td>
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<tr>
<td>Log octanol-water partition coefficient</td>
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</tr>
<tr>
<td>Vapour pressure</td>
<td>61 × 10^{-3} Pa at 25 °C (technical)</td>
</tr>
<tr>
<td></td>
<td>1.3 × 10^{-3} Pa at 25 °C (refined)</td>
</tr>
</tbody>
</table>

Organoleptic properties

A taste threshold of 500 µg/litre\(^1\) and an odour threshold of 0.5 µg/litre have been reported for chlordane in water (3).

\(^1\) Source: Hazardous Substances Data Bank, Bethesda, MD, National Library of Medicine, 1985 (NIH/EPA:OHM/TADS)
**Major uses**

Chlordane is a versatile, broad-spectrum contact insecticide used mainly for non-agricultural purposes (primarily for the protection of structures, but also on lawn and turf, ornamental trees, and drainage ditches). It is also used on corn, potatoes, and livestock. When used for termite control, it is applied to the soil by subsurface injection. Recently, the use of chlordane has been increasingly restricted in many countries (1,2,4).

**Environmental fate**

Chlordane is very resistant to chemical and biological degradation. It is highly immobile and migrates very poorly. Dissipation of chlordane from soils is mainly due to volatilization. The soil half-life is about 4 years (5). In spite of its very low mobility in soil, chlordane may be a low-level source of contamination in groundwater when applied by subsurface injection. Once in water bodies, it is not removed by photodegradation, hydrolysis, or biodegradation. Chlordane can be dissipated from surface water by volatilization, sorption to bottom and suspended sediments and particulates, and uptake by aquatic organisms (6,7).

15.8.2. Analytical methods

Chlordane can be determined by extraction with pentane followed by gas chromatography with electron-capture detection. The detection limit in tapwater and river water is about 0.01 µg/litre (8).

15.8.3. Environmental levels and human exposure

**Air**

Chlordane levels range from less than 0.1 to 60 ng/m$^3$ in urban air and from 0.01 to 1 ng/m$^3$ in rural air. It is a contaminant of indoor air when used for termite control; levels exceeding 1 µg/m$^3$ have been measured (2).

**Water**

In the USA, chlordane is rarely present in drinking-water; when found, it is mainly at levels below 0.1 µg/litre (6). Levels in drinking-water and groundwater higher than its solubility have been reported (4).

**Food**

Chlordane has been found in meat, eggs, and milk. Some chlordane metabolites have been found in human milk. Food is considered to be the major source of exposure of the general population (7).

15.8.4. Kinetics and metabolism in laboratory animals and humans

When cis-chlordane was administered orally, at least 2-8% of the dose was absorbed by rats and at least 30% by rabbits (9). It is also absorbed by the pulmonary and dermal routes in rats (10). Chlordane and its metabolites, mainly oxychlordane, are quickly distributed throughout the body and stored at the highest levels in adipose tissue (9). Oxychlordane has been detected in adipose tissue in the general human population (11).

Various faecal metabolites from both cis- and trans-chlordane have been identified. A metabolic scheme involving dehydrogenation, epoxidation, hydroxylation, and dechlorination reactions has been presented. A glucuronide conjugate was found in urine (12). Lactation is a route of excretion of chlordane in females; chlordane is present in breast milk mainly as oxychlordane (13).
15.8.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Chlordane is moderately toxic in acute exposure. Oral LD$_{50}$s of 335-430 mg/kg of body weight have been found in rats and mice, whereas in hamsters the oral LD$_{50}$ was 1720 mg/kg of body weight. Cows seem to be more sensitive, with oral LD$_{50}$s of 25-90 mg/kg of body weight. Acute exposure to chlordane produces ataxia, convulsions, respiratory failure, and cyanosis (7).

Long-term exposure

In a 2-year study, dogs fed chlordane at 0, 7.5, 75, 375, or 750 µg/kg of body weight per day showed altered liver enzyme activities and slightly increased relative liver weight at the two highest doses. The NOAEL in this study was 75 µg/kg of body weight per day (14).

F-344 rats (80 per sex per dose) were fed technical chlordane in the diet at 0, 1, 5, or 25 mg/kg for 130 weeks. Absolute and relative liver weights were increased in all treated groups as compared with controls. Serum bilirubin levels were increased in mid- and high-dose male rats. Histopathological examination revealed a significantly increased incidence of hepatocellular swelling in both sexes at the high dose and in some of the mid- and low-dose males. A NOAEL of 1 mg/kg of diet, or approximately 0.05 mg/kg of body weight per day, was indicated by this study (15).

Reproductive toxicity, embryotoxicity, and teratogenicity

Male rats exposed for 90 days to 19.5 mg/kg of diet (about 1 mg/kg of body weight per day) showed changes in the ventral prostate (16). Chlordane reduced litter viability and delayed growth in multigenerational studies in rats and mice; in these studies, the NOAEL was 30 mg/kg of diet and the LOAEL 50 mg/kg of diet. At lower doses, significant effects appeared only in the third and fourth generations (17,18). Effects were also seen in pups born to untreated dams but nursed by treated dams (17). Female mice exposed on days 1-19 of pregnancy to 8 mg/kg of body weight gave birth to apparently healthy progeny in which cell-mediated immunity was significantly reduced at adult age (19).

Mutagenicity and related end-points

Chlordane was positive in *Saccharomyces cerevisiae* for mitotic gene conversion after metabolic activation (20) and in maize for reverse mutation (21). It was mutagenic to Chinese hamster V79 cells and induced sister chromatid exchange in intestinal cells of fish treated in vivo (22). Chlordane was negative in *Bacillus subtilis* and *Salmonella typhimurium* for reverse mutation (21,23), in primary cultures of rat, mouse, and hamster hepatocytes for unscheduled DNA synthesis, and in mice for the dominant lethal assay (23,24). It was not mutagenic to cultures of human fibroblasts, and studies on DNA damage in transformed human cells yielded conflicting results (22).

Carcinogenicity

Chlordane gave positive results in carcinogenicity studies conducted in three strains of mice, one of which has a very low frequency of spontaneous liver lesions (25-27). In all of these studies, chlordane exposure resulted in very high incidences of hepatic carcinomas in both male and female mice. In carcinogenicity studies on three strains of rats, chlordane did not exhibit generally carcinogenic effects (27-29); however, it produced an increased incidence of hepatocellular adenomas in F-344 SPF male rats (30).

15.8.6. Effects on humans

Neurological symptoms, including headache, dizziness, vision problems, incoordination, irritability, excitability, weakness, muscle twitching, and convulsions, were consistently mentioned in a compilation of
case-reports and personal reports of humans accidentally exposed by inhalation or ingestion to unquantified concentrations of chlordane. A woman died 9 days after ingestion of 104 mg/kg of body weight (2). Following ingestion of drinking-water contaminated with chlordane at concentrations of up to 1.2 g/litre, 13 persons showed gastrointestinal and/or neurological symptoms (7).

15.8.7. Guideline value

IARC re-evaluated chlordane in 1991 and concluded that there was inadequate evidence for its carcinogenicity in humans and sufficient evidence for its carcinogenicity in animals, classifying it in Group 2B (22).

JMPR re-evaluated chlordane in 1986 and established an ADI of 0.5 µg/kg of body weight by applying an uncertainty factor of 100 to a NOAEL of 50 µg/kg of body weight per day derived from a long-term dietary study in rats (15).

Although levels of chlordane in food have been decreasing, it is highly persistent and has a high bioaccumulation potential. An allocation of 1% of the JMPR ADI to drinking-water gives a guideline value of 0.2 µg/litre (rounded figure).

References


28. *Chlordane chronic feeding study in mice*. Research Institute for Animal Science in Biochemistry and
Toxicology, 1983 (unpublished report for Velsicol Chemical Corporation, Chicago, IL).


15.9 Chlorotoluron

15.9.1. General description

Identity

CAS no.: 15545-48-9
Molecular formula: C_{10}H_{13}ClN_{2}O

The IUPAC name for chlorotoluron is 3-(3-chloro-\textit{p}-tolyl)-1,1-dimethylurea.

**Physicochemical properties (1)**

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<th>Property</th>
<th>Value</th>
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<tbody>
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<td>Physical state</td>
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<td>Melting point</td>
<td>147-148 °C</td>
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<td>Vapour pressure</td>
<td>$0.017 \times 10^{-3}$ Pa at 20 °C</td>
</tr>
<tr>
<td>Density</td>
<td>1.4 g/cm$^3$ at 20 °C</td>
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<td>Water solubility</td>
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</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>2.29</td>
</tr>
</tbody>
</table>

**Organoleptic properties**

No odour was detected at a concentration of 9.0 mg/litre (99.3% purity, dissolved in still, bottled water, equilibrated to 40 °C, eight assessors) (Water Research Centre, unpublished data, 1990).

**Major uses**

Chlorotoluron is a pre- or early post-emergence herbicide widely used to control annual grasses and broad-leaved weeds in winter cereals (1).

**Environmental fate**

Chlorotoluron is slowly degraded in water and is quite persistent. Chemical hydrolysis is not a significant degradation mechanism. However, it is degraded by photolysis in water and under laboratory conditions; the half-lives at pH 5, 7, and 9 at 22 °C were over 200 days. In another study, half-lives of approximately 120 and 80 days were reported for river and pond water (containing 1% sediment), respectively. Degradation proceeded via $N$-demethylation, yielding 3-(3-chloro-\textit{p}-tolyl)-1-methylurea as the major metabolite and some minor polar metabolites (Ciba-Geigy, unpublished data, 1989).

In laboratory studies, the rate of degradation of chlorotoluron in soil is slow and follows first-order kinetics. The estimated half-life in loamy sand and organic and peat soil is several months (2). Rates of degradation were nearly tripled by raising the temperature from 25 °C to 35 °C. Under field conditions, chlorotoluron appears to degrade at a higher rate. When applied in the spring on bare soil, it disappeared from the 0-5-cm soil layer with a half-life of 30-40 days; dissipation was slower in autumn (Ciba-Geigy,
15.9.2. Analytical methods

Chlorotoluron may be determined by separation with reverse-phase high-performance liquid chromatography followed by ultraviolet and electrochemical detection (3). Detection limits of 0.1 µg/litre have been reported (4). Gas chromatography/mass spectroscopy can also be used for the determination stage.

15.9.3. Environmental levels and human exposure

Air

Because of its low vapour pressure, chlorotoluron is unlikely to be a major contaminant in air.

Water

Chlorotoluron is slightly mobile in soil and likely to reach surface waters following agricultural application. It has occasionally been detected in waters in the United Kingdom at concentrations ranging from 0.4 to 0.6 µg/litre (5). In Germany, levels up to 1.2 µg/litre have been detected in drainage water from fields soon after normal treatment (Ciba-Geigy, unpublished data, 1989). In another German study, chlorotoluron was frequently detected in raw waters; concentrations of 0.2 and 0.3 µg/litre were reported for surface water and groundwater, respectively (6).

Food

It is generally considered that there is only limited exposure to chlorotoluron from food. In one study, residues of 0.04-0.08 and 0.06-0.35 mg/kg were detected in grain and straw samples, respectively (Ciba-Geigy, unpublished data, 1989). However, the majority of samples contained no measurable residues.

Estimated total exposure and relative contribution of drinking-water

Based on exposure from food and water, the estimated daily intake was 4.2 µg/person in a German study (Ciba-Geigy, unpublished data, 1989).

15.9.4. Kinetics and metabolism in laboratory animals and humans

Chlorotoluron is readily and rapidly absorbed when given orally. No evidence of its accumulation in any particular organ or tissue has been reported. In the rat, it is metabolized mainly via N-demethylation and stepwise oxidation of the ring methyl group to hydroxymethyl and carboxymethyl derivatives. At doses above 50 mg/kg, the phenylmethyl group is transformed to a methylthiomethyl group. Chlorotoluron is rapidly excreted in the urine in the form of metabolites, a negligible amount being excreted in expired air (Ciba-Geigy, unpublished data, 1989).

15.9.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Chlorotoluron is of low acute oral toxicity in various species; oral LD$_{50}$s range from 2700 to more than 10 000 mg/kg of body weight. The rat dermal LD$_{50}$ was more than 2000 mg/kg of body weight. It caused no eye or skin irritation in the rabbit or skin sensitization in the guinea-pig (7; Ciba-Geigy, unpublished data, 1989).
**Short-term exposure**

Short-term feeding studies in animals suggest that chlorotoluron is of low toxicity. Rats were fed chlorotoluron in the diet at doses of 0, 800, 3200, or 12,800 mg/kg for 3 months. At the highest dose, there was a slight decrease in body weight in both males and females and an increased incidence of splenic haemosiderosis and Kupffer’s cell activity in the liver. There were slight reversible increases in haemoglobin concentration, erythrocyte counts, and haematocrit values in females at 12,800 mg/kg and transient increases in serum alkaline phosphatase activity at 3200 and 12,800 mg/kg. The NOAEL was 800 mg/kg, equal to 52 mg/kg of body weight per day (Ciba-Geigy, unpublished data, 1989).

In a 3-month study, dogs were fed diets containing 0, 600, 2400, or 9200 mg of chlorotoluron per kg. Animals in the highest dose group died after 10 weeks from severe cachexia, resulting from starvation. At the two highest doses, there were decreases in food intake and body weights, but the only histopathological changes that could be related to treatment were increased incidence of splenic and hepatic haemosiderosis (Ciba-Geigy, unpublished data, 1989).

**Long-term exposure**

Mice were fed chlorotoluron in the diet at levels of 0, 100, 500, or 2500 mg/kg for 2 years. At 2500 mg/kg, there was a statistically significant reduction in body weight, a slight increase in white blood cell count, increased plasma urea levels, an increase in the activity of alkaline phosphatase in females, and a statistically significant reduction in the mean relative kidney weights in both sexes. There was a slightly increased concentration of albumin in males at 500 and 2500 mg/kg. The NOAEL for this study was 100 mg/kg, equivalent to 11.3 mg/kg of body weight per day (Ciba-Geigy, unpublished data, 1989).

In a 2-year study, rats were fed chlorotoluron in the diet at dose levels of 0, 100, 500, or 2500 mg/kg. Marked depression in body weight gain was observed at 2500 mg/kg, accompanied by a slight reduction in feed consumption. At the same dose level, slight increases in the incidence of spleen haemosiderosis in females and in aminotransferase activity in males were observed. The NOAEL for this study was 100 mg/kg, equivalent to a daily intake of 5 mg/kg of body weight (Ciba-Geigy, unpublished data, 1989).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Chlorotoluron was not teratogenic in rats at doses of up to 1000 mg/kg of body weight per day when administered by gavage on days 6-15 of gestation (Ciba-Geigy, unpublished data, 1989). A mild retardation in the ossification rate of the hindlimb was seen in the 1000 and 500 mg/kg groups; this was considered to be related to maternal toxicity.

In a two-generation study, chlorotoluron was administered orally to rats at dietary doses of 0, 300, 1000, or 3000 mg/kg. At 3000 mg/kg, there was a significant reduction in body weight and food consumption of both parents and offspring, a significantly reduced mean number of implantation sites per dam, and depressed locomotor activity in some pups. The NOAEL in this study was 300 mg/kg (Ciba-Geigy, unpublished data, 1989).

No changes were observed in the testes and spermatozoa of male rats given chlorotoluron intragastrically at doses of 0.2 or 2.0 mg/kg of body weight per day, 5 days per week for 10 weeks, although the offspring had lower body weights and body lengths. When the doses were administered in the feed, no effects were observed in the fetuses, indicating that the toxicity is affected by the method of administration (8).

**Mutagenicity and related end-points**

Chlorotoluron and its metabolites have shown no evidence of mutagenicity in a number of bacterial or in vitro and in vivo mammalian test systems (Ciba-Geigy, unpublished data, 1989).
Carcinogenicity

No carcinogenic effects were reported in rats exposed to doses of 0, 100, 500, or 2500 mg/kg in the diet for 2 years. However, in a 2-year dietary study, an increased incidence of adenomas and carcinomas of the kidney was reported in male mice at 2500 mg/kg. The incidence of hepatocellular carcinomas was also increased in male mice receiving 2500 mg/kg and slightly increased at 500 mg/kg. When the incidences of hepatocellular carcinomas and adenomas were combined, the total number of tumours remained within the historical control ranges. No carcinogenic effects were reported at 100 mg/kg of diet (Ciba-Geigy, unpublished data, 1989). These studies suggest that chlorotoluron has a carcinogenic potential that is both species- and sex-specific.

15.9.6. Effects on humans

No cases of human poisonings have been reported following chlorotoluron exposure.

15.9.7. Guideline value

Chlorotoluron is of low toxicity in acute, short-term, and long-term exposures in animals, but has been shown to cause an increase in adenomas and carcinomas of the kidney in male mice given high doses for 2 years. Chlorotoluron and its metabolites have shown no evidence of genotoxicity. In view of this, the guideline value can be calculated using a TDI approach.

The NOAEL in a 2-year feeding study in mice was 11.3 mg/kg of body weight per day (Ciba-Geigy, unpublished data, 1989). A TDI of 11.3 µg/kg of body weight can be calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for evidence of carcinogenicity). An allocation of 10% of the TDI to drinking-water results in the guideline value of 30 µg/litre (rounded figure).

References


15.10 DDT and its derivatives

15.10.1. General description

Identity

CAS no.: 107917-42-0
Molecular formula: C₁₄H₉Cl₅

The term DDT refers to \( p,p' \)-DDT, or \( p,p' \)-dichlorodiphenyl trichloroethane. The compound’s structure permits several different isomeric forms, such as \( o,p' \)-DDT. The term DDT is also applied to commercial products consisting predominantly of \( p,p' \)-DDT, but also containing smaller amounts of other compounds, including \( p,p' \)- and \( o,p' \)-DDD (dichlorodiphenyl dichloroethane) and \( p,p' \)- and \( o,p' \)-DDE (dichlorodiphenyl dichloroethene) (1).

Physicochemical properties (1)

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</tr>
</tbody>
</table>

Organoleptic properties

All DDT isomers are tasteless, almost odourless solids. The odour threshold for DDT in water is 0.35 mg/litre (2).

Major uses

DDT is a nonsystemic contact insecticide with a broad spectrum of activity (3). It was banned in several countries in the early 1970s, because of ecological considerations, and a number of developed countries have more recently restricted or banned its use except when it is needed for the protection of human health.

DDT is still used extensively for the control of yellow fever, sleeping sickness, typhus, malaria, and other insect-transmitted diseases. Without it, vast populations would suffer the ravages of endemic and epidemic malaria. Replacement of DDT by malathion or propoxur would increase the cost of malaria control considerably, forcing some countries to decrease the coverage of their control programmes (4).

Environmental fate

DDT and its metabolites are persistent in the environment and resistant to complete degradation by microorganisms, although photochemical degradation does occur. The persistence of DDT is substantially lower in tropical climates than in temperate ones (a few months as compared with years) (1).

DDT and its metabolites are readily adsorbed on to sediments and soils, which can act both as sinks and as long-term sources of exposure. Because of its strong tendency to be adsorbed on to surfaces, most DDT that enters water is and remains firmly attached to soil particles. If it does find its way into water, it is gradually lost by adsorption on to surfaces (1).

The physical and chemical properties of DDT and its metabolites enable these compounds to be taken up
readily by organisms from the surrounding medium and from food. In aquatic organisms, uptake from water is generally more important, whereas food is the major source for terrestrial fauna. High lipid solubility and low water solubility lead to the retention of DDT and its stable metabolites in fatty tissue. In general, organisms at higher trophic levels tend to contain more DDT-type compounds than those at lower ones. These compounds can be transported around the world in the bodies of animals, as well as in ocean and air currents (1).

15.10.2. Analytical methods

DDT and its metabolites may be determined in water by gas chromatography with electron-capture detection. The limits of detection are 60 ng/litre for \( p,p' \)-DDT, 10 ng/litre for \( p,p' \)-DDE, and 2.5 ng/litre for \( p,p' \)-DDD (3).

15.10.3. Environmental levels and human exposure

Air

When DDT is sprayed, any that fails to adhere to its target drifts away; vaporization from treated fields can be detected for more than 6 months after application. Although most of it settles in the same area, some drifts over long distances. Traces of DDT have been found in dust known to have drifted over 1000 km and in water produced by melting Antarctic snow.

With rare exceptions, concentrations of DDT in air in nonagricultural areas have been in the range <1-2.36 ng/m\(^3\). In agricultural communities, concentrations have ranged from 1 to 22 ng/m\(^3\). In communities with antimosquito fogging programmes, concentrations may be much higher, 8.5 \( \mu g/\text{m}^3 \) being the highest level recorded (4).

Water

In a study of surface waters in the USA during 1964-1968, the highest level recorded for a DDT-related compound was 0.84 \( \mu g/\text{litre} \). Concentrations in Germany were even lower, averaging 10 ng/litre and never going as high as 1 \( \mu g/\text{litre} \). The average concentrations of total DDT in drinking-water in Czechoslovakia were 11 and 15 ng/litre in 1972 and 1973, respectively. DDT was not detected (limit 0.01 ng/litre) in tapwater in a 1977 survey carried out in Ottawa (Canada) (4).

Within the Global Environment Monitoring System (GEMS) water network, DDT and its metabolites were found in some rivers during 1979-84. The following average concentrations were measured (5): India, 560 ng/litre; Italy, 3 ng/litre; Netherlands, <2 ng/litre; USA, 0.2 ng/litre; Canada and France, not detected.

Food

Daily intake of DDT from food has been measured in several countries. During 1985-88, in Australia, Finland, Guatemala, Japan, Thailand, the United Kingdom, and the USA, the reported mean daily dietary intake by the average adult was less than 2 \( \mu g \) (6). In Egypt, in 1988, a mean daily intake of 960 \( \mu g \) was reported for the average adult (7).

Human milk may contain a higher concentration of DDT than cows’ milk in the same country. So far, there is no evidence that this difference is of any significance for breast-fed babies, even where the concentration of DDT in human milk is comparatively high (4). The average concentration of total DDT in whole human milk in 15 countries between 1976 and 1986 ranged from 2 to 380 \( \mu g/\text{litre} \) (8). On the assumption that a 5-kg infant consumes 0.6 litres of milk per day, the intake at the highest concentration found would amount to about 200 \( \mu g/\text{day} \), or 40 \( \mu g/\text{kg} \) of body weight per day. It should be remembered that such intake is limited to a few months in a lifetime. Furthermore, neonates are not at increased risk, as they are not particularly susceptible to DDT’s adverse effects (9).
**Estimated total exposure and relative contribution of drinking-water**

It has been estimated that over 90% of the DDT stored in the general population is derived from food (4). In 1965, intake in the USA was approximately 40 µg/day per person from food, less than 46 ng/day from water, less than 60 ng/day from urban air, and less than 0.5 µg/day from air in small agricultural communities. Other investigators have also concluded that food is the major source of intake of DDT and related compounds for the general population (4).

**15.10.4. Kinetics and metabolism in laboratory animals and humans**

DDT is absorbed after inhalation and ingestion, the latter being the more important route of absorption. Absorption of small doses, such as those found in food residues, is virtually complete and is facilitated by the presence of fat in food. Even in solution, DDT is poorly absorbed through the skin.

Most of the known facts concerning the distribution, storage, and excretion of DDT have been demonstrated in humans as well as in laboratory animals. The compound is stored preferentially in fat, and its storage in organs and other tissues following repeated intake is proportional to their neutral fat content. However, uptake of DDT by fat is slow; therefore, much more is distributed to other tissues following a single, large dose, and much more to adipose tissue following many small doses. In spite of the affinity of DDT for adipose tissues, most of the DDT-related compounds in blood are carried by proteins, less than 1% being carried in the tiny droplets of fat normally present in the blood.

Following repeated doses, storage in adipose tissue increases rapidly at first and then more gradually until a steady state is reached. Storage is relatively less at higher dosages because excretion is relatively greater. In humans, the time necessary to reach storage equilibrium is at least 1 year. There is a gradual reduction in the amount of DDT stored in the tissues if exposure to the compound is discontinued.

Like most species, humans convert some DDT to DDE, which is stored even more avidly than the parent compound. A small amount of DDD, an intermediate in the formation of the main excretory product 2,2-bis(4-chlorophenyl)-ethanoic acid (DDA), may also be found in tissues. A number of other metabolites have been detected in laboratory animals but not in humans. Technical DDT is more readily excreted and less readily stored than \( p,p' \)-DDT because it contains 15-20% of \( o,p' \)-DDT (4).

**15.10.5. Effects on laboratory animals and in vitro test systems**

**Acute exposure**

The acute toxicity of DDT is high in insects (LD\(_{50}\) is 14 mg/kg of body weight) and lower in mammals (oral LD\(_{50}\): 150-400 mg/kg of body weight). Acute intoxication with DDT elicits symptoms mainly from the central nervous system, and death is usually caused by respiratory arrest. Large doses cause focal necrosis of liver cells in several species (3).

**Long-term exposure**

Long-term studies of oral administration have been performed in rats, mice, hamsters, dogs, and monkeys. The liver is one of the main target organs, and hepatic effects range from increased liver weights to cellular necrosis. The NOAEL for hepatic effects was 32 mg/kg of body weight per day for 78 weeks in rats and about 10 mg/kg of body weight per day when given to rhesus monkeys for 3.5-7.5 years (3).

Effects on the central nervous system, such as tremors and hyperactivity, are also associated with long-term exposure to DDT. Nervous symptoms were apparent at doses of 20 mg/kg of body weight per day in rats, whereas hamsters showed no clinical signs of neurotoxicity at doses of up to 40 mg/kg of body
weight per day for life (3,9).

Reproductive toxicity, embryotoxicity, and teratogenicity

Levels of DDT as high as 200 mg/kg of food that do not produce any sign of poisoning have not produced any adverse effects in rats and mice on fertility, gestation, viability, lactation, and the health of the progeny. Reproduction was normal in dogs receiving a dosage of 10 mg/kg of body weight per day, which is approximately equivalent to a dietary level of 500 mg/kg for this species (4).

Because of its estrogenic properties, DDT was considered as a possible cause of abortion in dairy cattle, but no evidence of a relationship was found. Except for the weak estrogenic properties of o,p'-DDT, the endocrine-related effects of DDT and its analogues are confined to the adrenal glands, and even these effects are now considered to be mainly secondary to microsomal enzyme induction in the liver (4).

No teratogenic effects of DDT have been observed in multigeneration studies of reproduction in several animal species (4).

Mutagenicity and related end-points

In most studies, DDT did not induce genotoxic effects in rodent or human cell systems, nor was it mutagenic to fungi or bacteria (3).

Carcinogenicity

DDT produces an increase in liver tumours in mice. However, the susceptibility of the mouse to the formation of liver tumours when exposed to it may be the consequence of major species differences in the metabolism of DDT and in the activation of chemical carcinogens by this species. Mice form more DDE than humans and other species; humans form more of the polar metabolite DDA. Indeed, DDE has been considered to be the metabolite responsible for carcinogenicity in mice (9).

Male and female Porton Wistar rats were fed 125, 250, or 500 mg of DDT per kg in the diet for life. No adverse effects were observed on body weight gain or growth or on the survival rate. The study showed slight increases in the incidence of hepatomas in females only at 250 and 500 mg/kg in the diet; the 125 mg/kg dose level was without effect, and no increase in the incidence of cancer was seen in males at any of these doses. No metastases of any kind were observed. JMPR concluded that the 125 mg/kg dose, equivalent to 6.25 mg/kg of body weight per day, was the NOAEL for tumorigenesis in the rat (9).

15.10.6. Effects on humans

Signs and symptoms reported following acute intoxication by DDT include nausea, vomiting, paraesthesia, dizziness, ataxia, confusion, tremor, and, in severe cases, convulsions (3).

Repeated exposure of workers for 25 years at an average dosage of 0.25 mg/kg of body weight per day was without any adverse effect, and this may be taken as a no-effect level for humans (9). Epidemiological observations of humans have not provided firm evidence that DDT has any reproductive or teratogenic effects. All epidemiological studies in humans have indicated that DDT is not carcinogenic (9).

15.10.7. Guideline value

IARC has concluded that there is insufficient evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of DDT (Group 2B) (3).

Based on NOAELs of 6.25 mg/kg of body weight per day in rats, 10 mg/kg of body weight per day in monkeys, and 0.25 mg/kg of body weight per day in humans, JMPR recommended an ADI for humans of
0.02 mg/kg of body weight (9). For adults, this ADI would provide a 500-fold margin of safety for the NOAEL of 10 mg/kg of body weight per day found in the study in monkeys. This ADI is used for the derivation of the guideline value.

Because infants and children may be exposed to greater amounts of chemicals in relation to their body weight and because of concern over the bioaccumulation of DDT, the guideline value was calculated on the basis of a 10-kg child drinking 1 litre of water per day. Moreover, because there is significant exposure to DDT by routes other than water, a 1% allocation of the ADI to drinking-water was chosen. This leads to a guideline value for DDT and metabolites in drinking-water of 2 µg/litre.

This guideline value exceeds the water solubility of DDT of 1 µg/litre. However, some DDT may be adsorbed on to the small amount of particulate matter present in drinking-water, so that the guideline value of 2 µg/litre could be reached under certain circumstances.

It should be emphasized that, as for all pesticides, the recommended guideline value for DDT in drinking-water is set at a level to protect human health; it may not be suitable for the protection of the environment or aquatic life. The benefits of DDT use in malaria and other vector-control programmes far outweigh any health risk from the presence of DDT in drinking-water.

References


15.11 1,2-Dibromo-3-chloropropane
15.11.1. General description

Identity

CAS no.: 96-12-8
Molecular formula: C₃H₅Br₂Cl

Physicochemical properties (1)

1 Conversion factor in air: 1 ppm = 9.67 mg/m³

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Organoleptic properties

The odour and taste thresholds for 1,2-dibromo-3-chloropropane (DBCP) in water are both 0.01 mg/litre (1).

Major uses

DBCP is used as a nematocidal fumigant (1).

Environmental fate

DBCP is expected to volatilize from surface water. It is highly persistent in soil and has been shown to remain there for more than 2 years. It is mobile in soil and may migrate to groundwater (1).

15.11.2. Analytical methods

DBCP is determined by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking-water (2). This method is applicable to the measurement of DBCP over a concentration range of 0.03-1500 µg/litre. Confirmation is by mass spectrometry (detection limit 0.2 µg/litre). A detection limit of 0.02 µg/litre is possible when gas chromatography and electron-capture detection are used (3).

15.11.3. Environmental levels and human exposure

Air

DBCP is a low-level contaminant in air (1).

Water

In a survey of drinking-water wells near locations where DBCP had been used within the previous 2 years, this compound was found at low (µg/litre) levels. In wells not used for drinking-water, it has been detected at levels of up to 20 µg/litre (1).
**Food**

DBCP has been identified as a contaminant in vegetables grown in soils treated with it (1).

15.11.4. Kinetics and metabolism in laboratory animals and humans

On the basis of excretion studies, absorption is expected to be high by the oral route. Distribution is primarily to the liver and kidneys (4). Transplacental transfer also appears to occur (5).

Metabolic pathways for DBCP may involve epihalohydrin, other reactive epoxides, or 2-bromoacrolein as intermediates. Urinary metabolites in rats include mercapturic acid conjugates, β-chlorolactic acid, β-bromolactic acid, and 2-bromoacrylic acid (1). Most DBCP is excreted by the urinary and faecal routes; smaller amounts are excreted in expired air. The urine is the predominant route for the elimination of metabolites (6).

15.11.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Acute oral LD₅₀s of 170, 410, and 440 mg/kg of body weight were reported for rats, mice, and rabbits, respectively (1).

Short-term exposure

Dietary administration of DBCP to rats for 90 days resulted in increased kidney weights at 2 mg/kg of body weight per day, reduced body weight gain at 15 mg/kg of body weight per day, increased liver weight at 45 mg/kg of body weight per day, and muscular weakness and increased mortality at 135 mg/kg of body weight per day. The NOAEL was 0.5 mg/kg of body weight per day (7).

In a study in which Sprague-Dawley rats were given DBCP in drinking-water at concentrations of 0, 5, 50, 100, or 200 mg/litre (approximately 0, 0.4, 3.2, 5.2, and 9.4 mg/kg of body weight) for 64 days, renal lesions, increased protein and glucose levels, and increased urinary specific gravity were apparent at the two highest doses (8).

Long-term exposure

In a chronic study in which mice and rats received DBCP by gavage, a dose-related increase in mortality and a high incidence of toxic tubular nephropathy were reported at time-weighted average doses of 78.6-149.3 mg/kg of body weight per day in mice and 10.7 and 20.7 mg/kg of body weight per day in rats (9). Lifetime treatment of Charles River CD rats with doses of 0, 0.2, 0.68, or 2 mg/kg of body weight per day in the diet resulted in kidney lesions in female rats and reduced body weight and organ weight changes in male rats given 2 mg/kg of body weight per day (10).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a study in which male Dutch rabbits (6 per group) were given DBCP at 0, 0.9, 1.9, 3.7, 7.5, or 15 mg/kg of body weight in drinking-water 5 days per week for 10 weeks, testis weights and sperm production decreased and follicle stimulating hormone levels increased at 15 mg/kg of body weight, mean seminiferous tubular diameter decreased at 7.5 mg/kg of body weight, and abnormal sperm morphology was observed at 1.9 mg/kg of body weight. The NOAEL was 0.9 mg/kg of body weight (11,12).

In a study in which DBCP was administered at 0.02, 0.2, 2, or 20 mg/kg of body weight per day in drinking-water to male and female Sprague-Dawley rats for 60 days before mating, throughout mating, during gestation, and during the first 5 days of lactation, fetal body weights, pup weights, and food and
water intake were reduced at the highest dose (13).

Administration of DBCP at 0, 25, 50, or 100 mg/kg of body weight by gavage in corn oil to male and female CD-1 mice during the premating period (7 days), cohabitation (98 days) and segregation (21 days) was without effect on reproduction in the F₀ generation; however, when treatment at 100 mg/kg of body weight was administered to the offspring of F₁ mice, organ weights were reduced (14).

Male Sprague-Dawley rats given DBCP in corn oil by gavage at doses of 0, 0.9, 1.9, 3.7, 7.5, or 15 mg/kg of body weight for 77 days and mated with untreated females on days 65-71 had decreased body and testis weights at 3.7 but not at 7.5 mg/kg of body weight. Daily spermatozoa production was significantly lower in vehicle controls than in controls not given corn oil (15).

No teratogenic effects were found in fetuses of pregnant Wistar rats treated with DBCP by gavage at 12.5, 25, or 50 mg/kg of body weight per day on days 6-15 of gestation (5). The dose of 50 mg/kg of body weight per day was fatal to embryos, and those of 25 and 50 mg/kg of body weight per day reduced maternal body weights.

**Mutagenicity and related end-points**

Technical-grade DBCP was mutagenic in *Salmonella typhimurium* strains TA1535, TA1530, TA100, and TA98 and in *Escherichia coli*, with and without metabolic activation (16-21). Results were negative with *Salmonella typhimurium* strains A-98, TA1537, and TA1538 (16,19,20). DBCP was positive in the recessive lethal assay, in a genetic crossing-over assay, and for chromosome breakage in *Drosophila melanogaster* (22-24). Results of a dominant lethal assay were positive in rats (25) but negative in mice (26). Positive results were obtained in a study on sister chromatid exchange in cultured Chinese hamster cells, for chromosomal aberrations in rats treated *in vivo*, and for unscheduled DNA synthesis in germ cells of prepubertal mice treated *in vivo* (26-28). Results were negative in the mouse specific locus test (29).

**Carcinogenicity**

In a chronic study in which Osborne-Mendel rats received time-weighted average doses by gavage of 10.7 and 20.7 mg/kg of body weight per day, highly significant dose-related increased incidences of squamous cell carcinoma of the forestomach in males and females and mammary adenocarcinoma in females were observed. Significant dose-related increased incidences of squamous cell carcinoma of the forestomach of male and female B6C3F₁ mice were found at time-weighted average doses of 78.6-149.3 mg/kg of body weight per day (9).

In a chronic dietary carcinogenicity bioassay in Charles River rats, high-dose (2.0 mg/kg of body weight per day) male and female rats had significantly increased incidences of carcinoma of the renal tubules and squamous cell carcinoma of the stomach. Male rats also showed an increase in liver tumours following exposure to DBCP for 104 weeks (10).

In a chronic inhalation study, dose-related increased incidences of nasal cavity tumours were found in male and female F344 rats and B6C3F₁ mice at DBCP concentrations of 5.8 or 29 mg/m³, 6 h per day, 5 days per week. The mice also had treatment-related increased incidences of pulmonary tumours (30).

DBCP was positive as a tumour initiator in the skin of Han/ICR Swiss mice but negative as a whole carcinogen for skin (31).

**15.11.6. Effects on humans**

Reduced spermatogenesis, which was reversible, was reported in chemical plant workers and agricultural workers exposed to DBCP (1). Possible permanent destruction of germinal epithelium was reported in a follow-up of exposed workers (32). No chromosomal aberrations were identified in men in whom
spermatogenesis was suppressed as a result of occupational exposure to DBCP, nor were there increases in abortions and malformations in offspring (33). Results were negative in an epidemiological study of the relationship between DBCP contamination of drinking-water and reproductive indices (e.g., birth rate, birth weight, birth defects) (34). Approximately 98% of 45,914 mothers were exposed to 3 µg/litre or less of DBCP.

No association was found between DBCP contamination of drinking-water (average levels 0.004-5.8 µg/litre) and incidences of gastric cancer and leukaemia (35); 14% of the areas concerned had levels greater than 1 µg/litre. These results differ from those of a similar earlier study that indicated a tentative association between DBCP exposure in drinking-water and gastric cancer and leukaemia (36). There was no association between cancer incidence and DBCP exposure in a cohort of 550 chemical workers potentially exposed to this compound during its production from 1957 to 1975 (37). Exposure levels were not estimated.

15.11.7. Guideline value

On the basis of data from studies on different strains of rats and mice, DBCP was determined to be carcinogenic in both sexes by the oral, inhalation, and dermal routes. It was also determined to be a reproductive toxicant in humans and several species of laboratory animals. IARC has classified DBCP in Group 2B (possible human carcinogen) based upon sufficient evidence of carcinogenicity in animals (38). Recent epidemiological evidence suggests an increase in cancer mortality in individuals exposed to high levels of DBCP. It was found to be genotoxic in a majority of in vitro and in vivo assays.

The linearized multistage model was applied to the data on the incidence of stomach, kidney, and liver tumours in the male rat in a 104-week dietary study (10). The concentrations in drinking-water relating to excess lifetime cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$ are 10, 1, and 0.1 µg/litre, respectively. The guideline values associated with these excess lifetime cancer risks are therefore 10, 1, and 0.1 µg/litre, respectively. An adequate margin of safety exists at these concentrations for the reproductive toxicity of DBCP. For a contaminated water supply, extensive treatment (e.g., air stripping followed by adsorption to granular activated carbon) would be required to reduce the level of DBCP to the guideline values.

References


7. Torkelson TR, Sadek SE, Rowe VK. Toxicologic investigations of 1,2-dibromo-3-chloropropane.


15.12 2,4-Dichlorophenoxyacetic acid (2,4-D)

15.12.1 General description

Identity

CAS no.: 94-75-7
Molecular formula: C₈H₆O₃Cl₂

Physicochemical properties (1, 2)

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Organoleptic properties

Some individuals may be able to detect 2,4-D in drinking-water by taste or odour at about 20 µg/litre (2).

Major uses

2,4-D is a systemic chlorophenoxy herbicide widely used throughout the world in the control of broad-leaved weeds in cereal cropland and on lawns, turf and pastures. It is also used to control aquatic weeds. Commercial 2,4-D products are marketed as alkali salts, amine salts, and ester formulations. Impurities may be present in the technical product as a result of the manufacturing process (1).

Environmental fate

2,4-D can enter the environment through effluents and spills arising from its manufacture and transport and through direct application as a weed-control agent. It is removed from the environment principally by biodegradation, the main degradation product being 2,4-dichlorophenol (3). The half-life of 2,4-D in soil is reported to range from 4-7 days in most soil types (4, 5) to up to 6 weeks in acidic soils (5, 7). It is rapidly biodegraded in water, although some may be degraded by photolysis near the surface. Half-lives in water range from one to several weeks under aerobic conditions and can exceed 120 days under anaerobic conditions (8). 2,4-D is not expected to accumulate in bottom sediments and muds. Except in some algae, it does not bioaccumulate in aquatic or terrestrial organisms because of its rapid degradation (9).

15.12.2 Analytical methods

Residues of 2,4-D in water are commonly measured by extraction, chemical derivatization, separation by gas-liquid chromatography, and electron-capture detection. This method is suitable for the detection of picogram levels (2). Electrolytic conductivity detection is also used; the detection limit is then 0.1 µg/litre (10).

15.12.3 Environmental levels and human exposure

Air

Residues of 2,4-D in the atmosphere are predominantly in the form of the isopropyl and butyl esters (8). In areas of Saskatchewan, Canada, where the herbicide was heavily used, 30% of ambient air samples collected from 1966 to 1975 contained less than 0.01 µg/m³, while 10% contained more than 1 µg/m³ (11). Average concentrations in air surveyed in Washington State, USA, in 1973 and 1974 ranged from 0.10 to
1.41 µg/m³; at 85% of the locations surveyed, average concentrations were less than 1.0 µg/m³ (12).

**Water**

2,4-D was detected, at a maximum concentration of 29 µg/litre in 52 of 805 samples of raw and treated drinking-water from municipal and private supplies in surveys conducted in six Canadian provinces from 1971 to 1986 (13). No residues were detected in drinking-water samples analysed routinely in market basket surveys (detection limit 5 µg/litre) in the USA (2). In Germany, 910 samples of raw and treated drinking-water contained no 2,4-D; 23 samples were above the detection limit (0.1 µg/litre) (Federal Environmental Office, unpublished data).

Of 447 samples of surface waters in three Canadian agricultural areas surveyed from 1981 to 1985, 78 had detectable 2,4-D concentrations; mean annual concentrations ranged from 0.01 to 0.7 µg/litre (10). 2,4-D was detected in 38.5% of 1386 surface water samples from the Canadian prairies tested between 1971 and 1977 (detection limit 0.004 µg/litre); mean levels were less than 0.3 µg/litre (14). Maximum concentrations of 0.3 µg/litre were measured in infiltrated river bank water in the Netherlands (15). Concentrations in groundwater in the range 0.4-0.7 µg/litre have been reported (16).

**Food**

No residues of 2,4-D ester were detected in a total diet study conducted in Canada in 1976 - 78 (detection limit 0.5 mg/kg) (17). The rate of occurrence of detectable 2,4-D residues in food samples in the USA surveyed from 1965 to 1980 ranged from 0 to 4.2%; all levels were below 0.2 mg/kg (2).

**Estimated total exposure and relative contribution of drinking-water**

Based on the maximum limits for pesticide residues established by the Codex Alimentarius Commission (18), the theoretical maximum daily intake of 2,4-D in food ranges from 0.03 to 0.4 mg/day for a 60-kg adult; the global mean is 0.1 mg/day (2 µg/kg of body weight per day). The intake found in a total diet study in the USA in 1987 was 0.1 ng/kg of body weight per day for females aged 60-65 years and less than 0.1 ng/kg of body weight per day for children aged 6-11 months and males aged 14-16 years (19).

**15.12.4 Kinetics and metabolism in laboratory animals and humans**

2,4-D administered orally as the free acid or salt is absorbed rapidly and almost completely in rats and humans (20, 21). The amine salt is also well absorbed in rats, calves, and pigs, but absorption is much slower and less complete for esters of 2,4-D, which are probably hydrolysed to the free acid before absorption (22).

After absorption in rats, 2,4-D is distributed throughout the body; peak concentrations are reached in blood after 3 h (23) and in kidney, liver, spleen, and lung after 6 h (22). In humans given an oral dose of 5 mg/kg of body weight, elimination was fairly rapid (half-time 17.7h); 82% was excreted unchanged in urine, and 13% as a conjugate (21). Similar results were observed in rats (24).

**15.12.5 Effects on laboratory animals and in vitro test systems**

**Acute exposure**

Oral LD₅₀S for 2,4-D, for the acid equivalent of the isoocetyl, isobutyl, butyl, and butoxyethanol esters, and for the sodium and dimethylamine salts range from 420 to 840 mg/kg of body weight in F344 rats (24). Similar results have been obtained for other species (2).
**Long-term exposure**

In a 2-year chronic toxicity study in Fischer 344 rats (60 per sex per dose), animals were fed 2,4-D in the diet at doses equivalent to 0, 1, 5, 15, or 45 mg/kg of body weight per day. Kidney weights were increased significantly in males and females at 45 mg/kg of body weight per day and in males at 15 mg/kg of body weight per day, and thyroid/parathyroid weights were increased significantly in males and females at 45 mg/kg of body weight per day and in females at 15 mg/kg of body weight per day. At doses of 5, 15, and 45 mg/kg of body weight per day, an increased incidence of brown pigment was observed in kidney tubular cells of both males and females, and renal transitional epithelial cell hyperplasia was observed in females at 45 mg/kg of body weight per day. An increased frequency of renal microcalculi was observed in males at 15 and 45 mg/kg of body weight per day and in females at 45 mg/kg of body weight per day. Vacuolization of the cytoplasm of the renal cortex was noted in females at 45 mg/kg of body weight per day. The NOAEL in this study was 1 mg/kg of body weight per day (25).

In a 2-year study in which B6C3F1 mice (60 per sex per dose) were fed 2,4-D in the diet at doses equivalent to 0, 1, 5, 15, or 45 mg/kg of body weight per day, the only evidence of an effect was an increase in cytoplasmic homogeneity of renal tubular epithelium in male mice at 5 mg/kg of body weight per day and above. The NOAEL was 1 mg/kg of body weight per day (26).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Fertility and litter size were not affected by doses of 2,4-D up to 1500 mg/kg of diet (about 75 mg/kg of body weight) in a three-generation study in rats, although pup survival was sharply reduced at this dose (27). In rats orally dosed with 2,4-D on days 6-15 of gestation, there were no effects on fertility, gestation, viability of pups, or neonatal growth at any dose up to 87.5 mg/kg of body weight, but administration of the isooctyl or propylene glycol butyl ethers at 75 or 87.5 mg/kg of body weight resulted in decreased viability of offspring (28). 2,4-D given to rats at 1000 mg/litre in drinking-water during and after pregnancy did not cause any effects on reproduction, but retarded growth and increased mortality were observed in the second generation given the same dose for 2 years (29). Abnormal spermatogenesis and reductions in testis and prostate weights were reported in rats given 87.5 mg/kg of body weight of 2,4-D butyl ether; no effects were seen at 37.5 mg/kg of body weight (30).

Administration of 2,4-D acid and its butyl, isooctyl, and butoxyethanol esters to rats on days 6 - 15 of gestation caused reduced fetal weights and increased the frequency of minor skeletal malformations at doses of 100 mg/kg of body weight or higher; this effect was noted only at 300 mg/kg of body weight for the dimethylamine salt (31). Embryotoxic and fetotoxic effects, including reduced fetal body weight, subcutaneous oedema, delayed ossification, and wavy ribs, were observed in rats given 2,4-D or its isooctyl and propylene glycol butyl ether esters at doses of 50 - 87.5 mg/kg of body weight on days 6 - 15 of gestation; neither 2,4-D nor its esters were teratogenic at any dose (28).

In mice, embryotoxicity, reduced fetal weight, and increased fetal mortality were observed at a dose of 221 mg/kg of body weight per day of 2,4-D, the isopropyl ester, and the isooctyl ester. Teratogenic effects (cleft palate) were observed at doses of 124 mg/kg of body weight or greater for 2,4-D but not for the esters (32).

**Mutagenicity and related end-points**

The results of short-term genotoxicity studies conducted to date have been largely negative, and it is concluded that 2,4-D is non-genotoxic. It was not mutagenic in a number of microbial assays on *Salmonella typhimurium*, *Bacillus subtilis*, and *Escherichia coli* (2, 33-35). The unscheduled DNA synthesis test gave negative results in rat hepatocytes (36) and in one of two tests on human fibro-blasts (37, 38). Sister chromatid exchange tests *in vitro* gave negative results in Chinese hamster ovary cells (39) and positive results in human lymphocytes (40); *in vivo* tests were negative in mice (41), rat lymphocytes (39), hamsters (39), and humans (42).
Carcinogenicity

2,4-D did not exhibit any carcinogenicity in three long-term studies in rats and mice (33, 34); however, these studies were inadequate for the evaluation of carcinogenicity (34, 43). In a bioassay conducted in B6C3F1 mice (26), there were no carcinogenic effects at any dose; however, the lack of toxic effects at all dose levels indicates that the maximum tolerated dose (MTD) was unlikely to have been reached, thus precluding an assessment of carcinogenicity. In a 2-year carcinogenicity bioassay in Fischer 344 rats (25), an increase in astrocytomas of the brain was observed in males at the highest dose (45 mg/kg of body weight per day), as well as a significant positive dose-related trend for this effect. Although the systemic toxicity noted in the study supports the conclusion that an MTD was reached, the US Environmental Protection Agency concluded that it had not, and requested that the studies in rats and in mice be repeated at the same and higher doses to clarify the status of 2,4-D with respect to its carcinogenicity to animals.

15.12.6 Effects on humans

Acute exposure

Symptoms of acute exposure to high doses of 2,4-D include effects on the gastrointestinal tract, such as nausea, vomiting, and diarrhoea, direct myotoxic effects, such as muscular weakness, stiffness, muscular spasms, and partial paralysis, effects on the kidney, pulmonary oedema, and effects on the central and peripheral nervous systems, including central nervous system depression, lethargy, slowed respiration, coma, and death (2).

Carcinogenicity

Most epidemiological studies conducted to date have dealt with multiple exposures to various chlorophenoxy herbicides.

In a series of case-referent studies conducted in Sweden in the late 1970s and early 1980s, strong associations were noted between soft-tissue sarcomas (STS) and multiple lymphomas, including Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL), and the use of chlorophenoxy herbicides by agricultural or forestry workers (44, 45). These studies served to focus attention on STS, HD and NHL as the outcomes of interest in subsequent case-referent and cohort studies.

The association between STS and chlorophenoxy use was not confirmed in other case-referent studies, including one that involved primarily 2,4-D exposure (46). Negative results were also obtained in several cohort studies carried out to investigate STS in occupationally exposed workers (47-49). No cohort was exposed solely or principally to 2,4-D, including the “2,4-D cohort” of 878 chemical workers engaged in its manufacture at a chemical plant in the USA, 75% of whom had also been exposed to 2,4,5-T (47). Because of the small size of most of the cohorts, little reliance can be placed on these results.

A weak link between NHL and chlorophenoxy exposure was found in several case-referent studies, only one of which, however, was specifically concerned with 2,4-D. In this study, the relative risk was not significant for those who used 2,4-D more than 21 days per year, but the trend towards increasing risk with increasing number of days of use was marginally significant, and the risk was highly significant for those who did not take precautionary measures to reduce exposure by changing clothing soon afterwards or washing immediately after handling the pesticide (50, 51). In a second study (576 cases of NHL), the relative risk increased from 1.1 for subjects with any past occupational exposure to chlorophenoxy herbicides (primarily 2,4-D and 2, 4, 5-T) to 1.7 for people occupationally exposed to such herbicides for at least 15 years (the minimum latency period) (52). In another study (200 cases), the relative risk of NHL from farm herbicide use was 1.4, indicating only a marginal association, but rose to 2.2 for farmers who had used chlorophenoxy herbicides at any time (almost all 2,4-D) and to 6.0 for those who had used
unspecified herbicides for more than 20 days per year. The trend towards increasing risk with increasing number of days of use per year was highly significant (46).

No excess risk was observed for NHL in any of the cohort studies on occupational exposure (47-49), although the cohorts were generally too small to provide any conclusive evidence, and all had been exposed to chlorophenoxy herbicides other than 2,4-D. In a recent cohort study on farmers in Saskatchewan (Canada), where 2,4-D is extensively used, it was found that the risk of NHL increased with the use of herbicides, as measured by the number of acres sprayed, but it was not possible to conclude that the association was with 2,4-D (53).

In a Swedish case-referent study on malignant lymphoma, the combined relative risk for HD and NHL was 4.8, rising to 7.0 for more than 90 days of total exposure to a mixture of chlorophenoxy herbicides (45). Apart from this study, there is little evidence of an increase in risk of HD as a result of exposure to chlorophenoxy herbicides, based on another case-referent study (46) and three cohort studies (47-49).

Chlorophenoxy herbicides as a group, including 2,4-D, have been classified by IARC in Group 2B (possibly carcinogenic to humans) (54). However, based on the studies considered here, it is not possible to determine the status of 2,4-D with respect to carcinogenicity, as almost all the populations studied were exposed to a mixture of chlorophenoxy herbicides. In the only study in which exposure was clearly to 2,4-D alone (51), the association was weak.

**Mutagenicity**

No significant elevations were observed in sister chromatid exchanges in forestry workers before, during, and after spraying of 2,4-D and MCPA (42). Similar results were obtained for the frequency of chromosomal aberrations in workers exposed to 2,4-D and MCPA (55).

### 15.12.7 Guideline value

IARC has classified chlorophenoxy herbicides in Group 2B (limited evidence for carcinogenicity in humans, inadequate evidence in animals) (54). However, it is not possible to evaluate the carcinogenic potential of 2,4-D on the basis of the available data; epidemiological studies provide limited evidence that occupational exposure to chlorophenoxy herbicides may cause cancer, and long-term studies in animals continue to show equivocal evidence for carcinogenicity, in one sex and species only. 2,4-D was found to be non-mutagenic in the limited number of studies conducted.

Because the data on the carcinogenic potential of 2,4-D are inadequate, and because 2,4-D has not been found to be genotoxic, the TDI approach can be used to calculate a guideline value for drinking-water. Based on a NOAEL of 1 mg/kg of body weight per day for effects on the kidney in 2-year studies in rats and mice (25, 26) and an uncertainty factor of 100 (for intra- and interspecies variation), a TDI of 10 µg/kg of body weight can be derived. The use of an additional uncertainty factor for carcinogenicity was considered unnecessary, as the NOAEL should provide a sufficient margin of safety with respect to the lowest dose that was associated with an increase in brain tumours in rats. The guideline value, based on an allocation of 10% of the TDI to drinking-water, is 30 µg/litre.

**References**


2. 2,4-Dichlorophenoxyacetic acid (2,4-D). Geneva, World Health Organization, 1984 (Environmental Health Criteria, No. 29).


9. 2,4-Dichlorophenoxyacetic acid (2,4-D) - environmental aspects. Geneva, World Health Organization, 1989 (Environmental Health Criteria, No. 84).


21. Sauerhoff MW et al. The fate of 2,4-dichlorophenoxyacetic acid (2,4-D) following oral administration to man. *Toxicology*, 1977, 8:3-11.


28. Schwetz BA, Sparschu GL, Gehring PJ. The effect of 2,4-dichlorophenoxyacetic acid (2,4-D) and esters of 2,4-D on rat embryonal, foetal and neonatal growth and development. *Food and cosmetics toxicology*, 1971, 9:801-817.


36. Probst GS et al. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: a


42. Linnainmaa K. Sister chromatid exchanges among workers occupationally exposed to phenoxy acid herbicides 2,4-D and MCPA. *Teratogenesis, carcinogenesis, and mutagenesis*, 1983, 3:269-279.


15.13 1,2-Dichloropropane

15.13.1 General description

**Identity**

CAS no.: 78-87-5  
Molecular formula: C₃H₆Cl₂

**Physicochemical properties (1, 2)¹**

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<td>Log octanol - water partition coefficient</td>
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</table>

¹ Conversion factor in air: 1 ppm = 4.76 mg/m³.

**Organooleptic properties**

1,2-Dichloropropane has a chloroform-like odour. The odour threshold in water is 10 µg/litre (2).

**Major uses**

1,2-Dichloropropane, or propylene dichloride, is used primarily as a chemical intermediate, lead scavenger for antiknock fluids, dry-cleaning solvent, soil fumigant, scouring compound, spotting agent, and metal-degreasing agent (1).

**Environmental fate**

1,2-Dichloropropane is degraded in air by photochemically produced hydroxyl radicals; the half-life is 23 days or more. Direct photolysis probably does not occur. In water, it is relatively resistant to hydrolysis and has a half-life of 25-200 weeks. It volatilizes from surface waters. Its relatively low soil adsorption coefficient and high water solubility suggest that it is not appreciably adsorbed on to soil but migrates from it to groundwater. Little or no degradation in soil has been reported. Bioconcentration in animals or food-chains is unlikely to occur (2).
15.13.2 Analytical methods

1,2-Dichloropropane is usually determined by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking-water (3, 4). Confirmatory analysis is by mass spectrometry or halide-specific detectors (detection limit 0.03-0.2 µg/litre) (2).

15.13.3 Environmental levels and human exposure

Air

Median concentrations of 1,2-dichloropropane were reported to be 0.0 µg/m^3 in rural/remote areas, 0.26 µg/m^3 in urban/suburban areas, and 0.55 µg/m^3 in source-dominated areas (5).

Water

1,2-Dichloropropane was detected in samples from six of 466 randomly selected US groundwater supply systems in the USA from 1980 to 1981; levels ranged from 0.48 to 21 µg/litre (mean 0.86 µg/litre). It was also detected in seven of 479 systems with a high potential for contamination, at concentrations ranging from 0.21 to 18 µg/litre (mean 0.84 µg/litre; the detection limit was 0.2 µg/litre) (6). Most samples of raw, treated, and tapwater from the Great Lakes collected from the mid-1970s to early 1985 contained levels of 1,2-dichloropropane near or below the detection limit (7).


Estimated total exposure and relative contribution of drinking-water

At an air concentration of 0.26 µg/m^3, the exposure will be 5.2 µg/day for an adult with an air intake of 20 m^3/day. At a concentration of 0.86 µg/litre in drinking-water, the daily exposure for an adult consuming 2 litres of water per day is 1.7 µg.

15.13.4 Kinetics and metabolism in laboratory animals and humans

Studies in rats indicate that 1,2-dichloropropane is readily absorbed from the gastrointestinal tract (8, 9). Two days after the administration of [14C] 1,2-dichloropropane to rats by gavage, the highest concentrations of the radiolabel were detected in the liver, kidney, and blood (10).

It has been suggested that, in rats, 1,2-dichloropropane is dechlorinated and oxidized to epoxide intermediates, which are then hydrolysed and conjugated to form N-acetyl-S-(2-hydroxypropyl) cysteine. β-Chloroacetate, lactate, carbon dioxide, and oxalate have been identified as other metabolites (10). 1,2-Dichloropropane and its metabolites were eliminated by orally dosed rats in the urine (50%), faeces (5%), and expired air (30%) in the first 24 h after dosing (8).

15.13.5 Effects on laboratory animals and in vitro test systems

Acute exposure

LD_{50}s for 1,2-dichloropropane were reported to be 1000-2200 mg/kg of body weight in rats (oral), 500 mg/kg of body weight in mice (oral), 9224 mg/m^3 in rats (inhalation), and 10 200 mg/kg of body weight in rabbits (dermal) (11-13). In dogs, oral doses of 250 or 350 mg/kg of body weight produced gastrointestinal irritation, 580 mg/kg of body weight produced swelling of the epithelial cells of the kidney tubules and fatty infiltration in the convoluted tubules, and 5800 mg/kg of body weight resulted in incoordination and partial narcosis (14).
**Short-term exposure**

1,2-Dichloropropane doses of 0, 100, 250, 500, or 1000 mg/kg of body weight per day were administered to rats for 1, 5, or 10 days. Mild anaemia, liver necrosis, and decreased body weight gain were reported at 250 mg/kg of body weight per day, more severe anaemia at 500 mg/kg of body weight per day, and elevated blood urea levels at 1000 mg/kg of body weight per day. No effects were observed at 100 mg/kg of body weight per day (15).

When rats were given oral doses of 1,2-dichloropropane at 14.5 or 360 mg/kg of body weight per day for 30 days, levels of serum cholesterol, betalipoprotein, and gamma-globulin were increased, serum cholinesterase activity was inhibited, and the activities of fructose-1-monophosphate aldolase, alanine aminotransferase, and aspartate aminotransferase were increased (16). Rats given 1,2-dichloropropane orally at 8.8, 44, or 220 mg/kg of body weight per day for 20 days showed disturbances in protein formation, hepatic enzyme levels, and lipid metabolism (11).

Rats given 1,2-dichloropropane orally at 8.8, 44, or 220 mg/kg of body weight per day for 20 days showed disturbances in protein formation, hepatic enzyme levels, and lipid metabolism (11).

**Long-term exposure**

Groups of F344 rats were dosed by gavage with 1,2-dichloropropane in corn oil at 0, 125, or 250 mg/kg of body weight per day (females) and 0, 62, or 125 mg/kg of body weight per day (males), 5 days per week for 103 weeks. Females in the highest dose group showed decreased survival, increased incidence of liver lesions (focal and centrilobular necrosis), and decreased mean body weight. Rats exposed to 125 mg/kg of body weight per day showed decreased mean body weight (males) and an increased incidence of mammary gland hyperplasia (females). The NOAEL was 62 mg/kg of body weight per day in male rats, and the LOAEL was 125 mg/kg of body weight per day for both sexes (12).

In the same study, groups of B6C3F1 male and female mice were exposed to 1,2-dichloropropane at 0, 125, or 250 mg/kg of body weight per day. The decrease in survival rate in treated females was attributed in part to a high incidence of severe respiratory tract infection. The only other non-neoplastic effect observed was an increased incidence of liver lesions (hepatomegaly, focal and centrilobular necrosis) in treated males. The LOAEL was 125 mg/kg of body weight per day (12).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

In a 13-week study in which rats were given 1,2-dichloropropane at 0, 100, 250, 500, or 750 mg/kg of body weight per day by gavage 5 times per week, rats exposed at the two highest dose levels showed testicular degeneration and an increased number of degenerate spermatogonia in the epididymis (15). Doses of 0, 30, or 125 mg/kg of body weight per day administered to pregnant rats on days 6-21 of gestation did not affect the number of implantation sites, pregnancies, resorptions, or fetuses. However,
an increased incidence of delayed ossification of the skull was observed in the fetuses of the highest dose group (17).

**Mutagenicity and related end-points**

When tested with and without metabolic activation, 1,2-dichloropropane was mutagenic in *Salmonella typhimurium* (12, 18, 19). It was also mutagenic in *Aspergillus nidulans* when tested with activation by a rat liver homogenate (S9 fraction) but did not cause forward mutation in *Salmonella coelicolor* when tested without activation (18, 19). Sister chromatid exchanges and chromosomal aberrations were induced in Chinese hamster ovary cells exposed to 1,2-dichloropropane *in vitro* or without metabolic activation (12).

**Carcinogenicity**

1,2-Dichloropropane induced a significant increase in the incidence of hepatocellular neoplasms, primarily adenomas, in male and female B6C3F1 mice given doses of 125 or 250 mg/kg of body weight per day. There was no statistically significant increase in the incidence of any specific tumour type in F344 rats; however, there was a marginal but statistically significant increased incidence of mammary adenocarcinomas in female rats given 250 mg/kg of body weight per day. This was considered to be equivocal evidence for Carcinogenicity in the female rat (12).

**15.13.6 Effects on humans**

Clinical signs following the ingestion of 1,2-dichloropropane typically involve effects on the gastrointestinal system (nausea, burning, and vomiting), central nervous system (dizziness, disorientation, headache, and coma), kidney failure, and liver necrosis. Effects on the respiratory system, heart, and blood have also been described (2).

**15.13.7 Provisional guideline value**

IARC has classified 1,2-dichloropropane in Group 3 (not classifiable as to its Carcinogenicity in humans), as there are no human data and only limited data from animal studies (20).

A LOAEL of 100 mg/kg of body weight per day was identified on the basis of a variety of systemic effects in a 13-week oral study in rats (administration 5 days per week) (15). Use of an uncertainty factor of 10 000 (100 for intra- and interspecies variation, 10 for use of a LOAEL instead of a NOAEL, and 10 to reflect the limited evidence of Carcinogenicity in animals and a limited toxicity database, particularly for reproductive effects) gives a TDI of 7.14 µg/kg of body weight. With an allocation of 10% of the TDI to drinking-water, the provisional guideline value is 20 µg/litre (rounded figure).

**References**


15.14 1,3-Dichloropropane

15.14.1. General description

Identity

CAS no.: 142-28-9
Molecular formula: C₃H₆Cl₂

Physicochemical properties (1)¹

¹ Conversion factor in air: 1 ppm = 4.62 mg/m³

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Major uses

1,3-Dichloropropane is used as an alkylating agent, ring-forming agent, and polymerization catalyst or promoter in the synthesis of organic chemicals (2). It may be found as a contaminant of soil fumigants containing 1,3-dichloropropene.

15.14.2. Analytical methods

1,3-Dichloropropane is determined by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking-water (3). Mass spectrometry is used for confirmation; the detection limit is 0.10 µg/litre (4).

15.14.3. Environmental levels and human exposure

Water

In the Ohio River and its tributaries, 1,3-dichloropropane was detected at levels below 0.8 µg/litre (2). No data on levels in drinking-water were found in the available literature.

15.14.4. Effects on laboratory animals and in vitro test systems

Acute exposure

An oral LD₅₀ of 3.0 g/kg of body weight for 1,3-dichloropropane was reported in dogs (5). An LD₅₀ of 3.6 g/kg of body weight was reported in mice for an unspecified route of exposure; the slight inflammation of the digestive tract noted suggests that it may have been oral (6).

Short-term exposure

1,3-Dichloropropane induced mild dermatitis on the shaved dorsal skin of mice. Peripheral blood changes, including an increased number of leukocytes and reticulocytes, were observed in dermally exposed animals (7).

Mutagenicity and related end-points
1,3-Dichloropropane was mutagenic in *Salmonella typhimurium* strain TA100 with and without metabolic activation at concentrations of 10 µmol per plate or more (8). It was also mutagenic in *S. typhimurium* strain TA1535 with but not without metabolic activation. The compound was not mutagenic with or without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1537, and TA1538; *Escherichia coli* strains WP2 and WP2 uvr A; or *Saccharomyces cerevisiae* strain JD5 (9).

15.14.5. Conclusions

There is some indication that 1,3-dichloropropane may be genotoxic in bacterial systems. However, no short-term, long-term, reproductive, or developmental toxicity data pertinent to exposure via drinking-water could be located for this compound. The available data were considered to be insufficient to permit recommendation of a guideline value.

References


15.15 1,3-Dichloropropene

15.15.1. General description

**Identity**

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The molecular formula is C₃H₄Cl₂.

**Physicochemical properties (1,2)**

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</table>

1 Data also from Dow Chemical Company. Conversion factor in air: 1 ppm = 4.54 mg/m³

**Major uses**

1,3-Dichloropropene is a broad-spectrum soil fumigant used primarily for nematode control on crops grown in sandy soils.

**Environmental fate**

1,3-Dichloropropene is released to the environment when used as a fumigant. It volatilizes from both soil and surface waters to the atmosphere, where it can be photolytically degraded. Hydrolysis and microbial biodegradation also remove it from the environment (2).

**15.15.2. Analytical methods**

EPA Methods 524.2 (3) and 502.2 (4), which are standard purge-and-trap capillary-column gas chromatographic techniques for volatile organic compounds in water, should be suitable for the analysis of 1,3-dichloropropene. The detection limits for the compound are believed to range from 0.02 to 0.05 µg/litre.

**15.15.3. Environmental levels and human exposure**

**Water**

1,3-Dichloropropene was found in 41 of 1088 surface water samples and in 10 of 3949 groundwater samples in the USA. The 85th percentile values for all samples containing detectable levels of 1,3-dichloropropene were 1.3 µg/litre in surface water and 3.4 µg/litre in groundwater.¹ These data have not been validated and must therefore be accepted with caution.

¹ STORET water quality file. US Environmental Protection Agency, Office of Water (data file search conducted in May 1988).

**15.15.4. Kinetics and metabolism in laboratory animals and humans**

1,3-Dichloropropene is absorbed through skin and respiratory and gastrointestinal systems (1). Oral administration in rats resulted in approximately 90% absorption of the administered dose (5). Both cis- and trans-1,3-dichloropropene administered orally in rats were excreted primarily in the urine in 24-48 h (5,6). cis-1,3-Dichloropropene is probably biotransformed into an intermediate glutathione conjugate, and then follows the mercapturic acid pathway, and is excreted in the urine as a cysteine derivative. The main urinary metabolite (92%) of cis-1,3-dichloropropene was N-acetyl-S-[(c/s)-3-chloroprop-2-enyl]cysteine (6).

**15.15.5. Effects on laboratory animals and in vitro test systems**
Acute exposure

The acute oral LD₅₀s of 1,3-dichloropropene in male and female rats are 713 and 740 mg/kg of body weight, respectively (7). In mice, the oral LD₅₀ is 640 mg/kg of body weight. The dermal LD₅₀ in rabbits ranges from 504 to 2100 mg/kg of body weight (8).

Short-term exposure

Exposure of rats to 1,3-dichloropropene by gavage (10 or 30 mg/kg, 6 days per week, for 13 weeks) resulted in increased kidney weight (9). Exposure by inhalation to 13.6 mg/m³, 7 h per day, 5 days per week, for 6 months, resulted in discoloration of kidney and swelling of renal tubular epithelium (7).

Long-term exposure

Hyperplasia of the urinary bladder epithelium was observed as a result of inhalation exposure of B6C3F₁ mice to 1,3-dichloropropene at doses of 91 or 270 mg/m³, 6 h per day, 5 days per week for 24 months (10). Hyperplasia of the urinary bladder epithelium and kidney hydronephrosis were seen in B6C3F₁ mice after gavage exposure to Telone II (in which 1,3-dichloropropene is the active ingredient) in corn oil at doses of 0, 50, or 100 mg/kg of body weight, 3 times per week for 104 weeks (11).

Reproductive toxicity, embryotoxicity, and teratogenicity

No studies on the reproductive toxicity of 1,3-dichloropropene by the oral route of administration are available. In a study in which male and female Wistar rats were exposed to technical D-D (28% cis isomer, 27% trans isomer) by inhalation at 0, 64, 145, or 443 mg/m³ for 10 weeks, male and female mating, fertility, and reproductive indices were unaffected, litter sizes and weights were normal, and pup survival over 4 days was not affected (12). In a study of the effects of inhalation exposure to 1,3-dichloropropene on fetal development, pregnant Fischer 344 rats were exposed to 0, 91, 270, or 540 mg/m³ 1,3-dichloropropene for 6 h per day on gestation days 6-15. Effects included dose-related depression of maternal body weight gain, significant depression of feed consumption, decreases in water consumption at 540 mg/m³, and significant increases in relative kidney weights and decreases in absolute liver weights at 270 mg/m³ (13).

Mutagenicity and related end-points

Tests of commercial formulations containing 1,3-dichloropropene or a mixture of pure cis- and trans-1,3-dichloropropene (14), and pure cis-1,3-dichloropropene (15) were positive in Salmonella typhimurium strains TA1535 and TA100 with and without metabolic activation, indicating that 1,3-dichloropropene is a direct-acting mutagen. Positive results have also been reported in TA1978 (with and without metabolic activation) for a commercial mixture of 1,3-dichloropropene and a mixture of the pure isomers (14). 1,3-Dichloropropene was negative in a reverse-mutation assay with Escherichia coli B/r Wp2 and in the mouse host-mediated test with S. typhimurium G46 (16).

Carcinogenicity

F344 rats were gavaged 3 times per week with Telone II in corn oil at doses of 0, 25, or 50 mg/kg of body weight (77 per sex per dose: 52 per sex per dose gavaged for 104 weeks in the main carcinogenicity study, plus 5 per sex per dose sacrificed after 9, 16, 21, 24, and 27 months of exposure to 1,3-dichloropropene in an ancillary study). There was no increase in mortality in treated animals. Neoplastic lesions included squamous cell papillomas of the forestomach (male rats: 1/52; 1/52; 9/52; female rats: 0/52; 2/52; 3/52), squamous cell carcinomas of the forestomach (male rats: 0/52; 0/52; 4/52), and neoplastic nodules of the liver (male rats: 1/52; 6/52; 7/52). The increased incidence of forestomach tumors was accompanied by a positive trend for forestomach basal cell hyperplasia in male and female
rats of both treated groups. The highest dose level tested in rats (50 mg/kg of body weight) was approximately the maximum tolerated dose level (11).

B6C3F₁ mice (50 per sex per dose) were gavaged with Telone II in corn oil at doses of 0, 50, or 100 mg/kg of body weight, three times per week for 104 weeks. Because of excessive mortality from myocardial inflammation in control male mice approximately 1 year after the initiation of the study, conclusions concerning carcinogenicity were based on concurrent and National Toxicology Program (NTP) historical control data. Neoplastic lesions in female mice included squamous cell papillomas of the forestomach (0/50; 1/50; 2/50), squamous cell carcinomas of the forestomach (0/50; 0/50; 2/50), transitional-cell carcinomas of the urinary bladder (0/50; 8/50; 21/48), and alveolar/bronchiolar adenomas (0/50; 3/50; 8/50). The increased incidence of forestomach tumours was accompanied by an increased incidence of stomach epithelial cell hyperplasia in males and females at 100 mg/kg of body weight, and the increased incidence of transitional-cell carcinoma of the urinary bladder was accompanied by a positive trend for bladder hyperplasia in male and female mice of both treated groups. Incidences of neoplasms were not significantly increased in male mice (11).

In the NTP gavage studies (11), epichlorohydrin (1%), which can cause papillomas, carcinomas, and hyperplasia of the forestomach (17), was added as a stabilizer. It is possible that the gavage dosing procedure adopted in the NTP study produced epichlorohydrin concentrations at the site of application similar to those in the drinking-water study (17), albeit for much shorter periods. If this is true, it is possible that epichlorohydrin was involved in the development of the papillomas and carcinomas of the forestomach during the NTP study.

Exposure of Fischer 344 rats for 2 years to vapours of Telone II (0, 23, 91, and 270 mg/m³) did not result in increases in tumour incidence (18). The only tumorigenic effect of a similar exposure of B6C3F₁ mice was an increased incidence in benign lung tumours (bronchioloalveolar adenomas) in males exposed to 270 mg/m³ (10).

15.15.6. Effects on humans

The only known human fatality occurred a few hours after the accidental ingestion of a D-D mixture at an unknown dosage. The symptoms were abdominal pain, vomiting, muscle twitching, and pulmonary oedema. Treatment by gastric lavage failed. Inhalation of 1,3-dichloropropene at concentrations above 6.8 g/m³ resulted in gasping, coughing, substernal pain, and extreme respiratory distress (19).

A total of 64 male workers exposed to three compounds, including 1,3-dichloropropene, were evaluated to determine whether fertility was adversely affected. The exposed study population was divided into groups with up to 5 and more than 5 years of exposure. Sperm counts and percentage of normal sperm forms were the major variables evaluated. No adverse effects on fertility were observed (20), but the study participation rate for the exposed group was only 64%.

15.15.7. Guideline value

IARC concluded that there was sufficient evidence for the carcinogenicity of 1,3-dichloropropene in experimental animals to classify it in Group 2B (possible human carcinogen) (21). It is also a direct-acting mutagen. Based on observation of lung and bladder tumours in female mice in a 2-year NTP gavage study (11) and using the linearized multistage model, the drinking-water concentrations (and hence the guideline values) associated with excess lifetime cancer risks of 10⁻⁴, 10⁻⁵, and 10⁻⁶ are estimated to be 200, 20, and 2 µg/litre, respectively.

References¹

¹ References marked with an asterisk are confidential business information submitted to the Office of Pesticide Programs of the US Environmental Protection Agency.


6. Climie IJG, Morrison BJ. Metabolism studies on (Z),3-dichloropropene in the rat: group research report. Shell Research Ltd, 1978 (unpublished study TLGR.010178 submitted by Dow Chemical Company, Midland, MI; MRID 32984).*


15. Brooks TM, Dean BJ, Wright AS. Toxicity studies with dichloropropenes: mutation studies with 1,3-D and cis-1,3-dichloropropene and the influence of glutathione on the mutagenicity of cis-1,3-dichloropropene in Salmonella typhimurium: group research report. Shell Research Ltd, 1978 (unpublished study TLGR.0081 78, by Shell Chemical Co., Washington, DC; MRID 61059).*


15.16 Ethylene dibromide

15.16.1 General description

**Identity**

CAS no.: 106-93-4  
Molecular formula: C₂H₄Br₂

The IUPAC name for ethylene dibromide (EDB) is 1,2-dibromoethane.

**Physicochemical properties**

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<th>Value</th>
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<tr>
<td>Boiling point</td>
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</tr>
<tr>
<td>Density</td>
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<tr>
<td>Water solubility</td>
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<tr>
<td>Octanol-water partition coefficient</td>
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</tr>
<tr>
<td>Vapour pressure</td>
<td>1.5 kPa at 20 °C</td>
</tr>
</tbody>
</table>

**Major uses**

EDB is used as a fumigant against pests, certain insects, and nematodes (1), although its use for this purpose has been restricted or prohibited in several countries. Its main use is in leaded petrol, but it is also used to a lesser extent in solvents, waterproofing preparations, and medicine (2).

**Environmental fate**

Evaporated EDB in the atmosphere reacts with photochemically produced hydroxyl radicals; the half-life is 32 days (3).

In surface water, evaporation plays an important role in the removal of EDB; the half-life is in the range 1 -
5 days. It is very stable in groundwater, especially under anaerobic conditions, with an estimated half-life of about 20 years at 10 °C. Hydrolysis of EDB to bromide, ethylene, ethylene glycol, and carbon dioxide takes place in soil. Formation of vinyl bromide has so far been seen only under laboratory conditions (2,3).

15.16.2 Analytical methods

Gas-phase extraction followed by gas chromatography with electron-capture detection is used for the determination of EDB. The method is capable of achieving a detection limit in tapwater and river water of about 0.01 µg/litre (4).

15.16.3 Environmental levels and human exposure

Air

In the USA, concentrations of EDB in air of less than 0.6 ng/m³ in rural areas and 80 - 460 ng/m³ (mean 200 ng/m³) in urban and suburban areas were reported (4).

Water

EDB is found mainly in groundwater as a result of petrol spills and agricultural use. In groundwater in agricultural areas, levels of 0.01-15 µg/litre have been reported (2).

Food

EDB may be present in treated foods depending on the treatment and storage conditions. It is found in grain, oats, and fruits at mg/kg levels and in white and wholemeal bread at µg/kg levels (3).

15.16.4 Kinetics and metabolism in laboratory animals and humans

EDB is readily absorbed following oral, dermal, and inhalation exposure in rats and pigs (5, 6). After ingestion, the concentration of metabolites is highest in the liver and kidney (6). In the rat, two main metabolic pathways lead to the formation of the metabolites that seem to be responsible for the biological effects of EDB. 2-Bromoacet-aldehyde, which is formed via the oxidative pathway, is associated with some histopathological changes, such as liver damage (6, 7). Another metabolite is formed via the conjugative pathway and is believed to be responsible for binding to DNA and, hence, mutagenesis. Four times as much EDB in metabolized via the oxidative pathway as by the conjugative one (6). In pigs, rats and mice, the metabolites are excreted mainly in the urine (6).

15.16.5 Effects on laboratory animals and in vitro test systems

Acute exposure

When EDB was administered orally, acute LD₅₀s were found to be 117-146 mg/kg of body weight for rats, 110 mg/kg of body weight for guinea-pigs, and 55 mg/kg of body weight for female rabbits (6).

Long-term exposure

In a 2-year gavage study in rats and mice, non-neoplastic effects were found in the forestomach (hyperkeratosis) and testes (atrophy) of both species and in the liver (hepatitis) and renal cortex (degeneration) of rats (8). In chronic inhalation studies in F344 rats and B6C3F₁ mice, EDB administration was associated with increased mortality and non-cancerous lesions of the respiratory system (inflammation, epithelial hyperplasia, squamous metaplasia) in both species and liver necrosis, kidney nephropathy, and degeneration of the testes, adrenal cortex, and retina in rats (9).
Reproductive toxicity, embryotoxicity, and teratogenicity

Oral administration of EDB to bulls at doses of 4 mg/kg of body weight per day for 2-3 weeks resulted in the formation of abnormal spermatozoa. Doses of 2 mg/kg of body weight per day had no effect on the reproductive capacity of cows and ewes (6). Hens given feed containing 50-320 mg of EDB per kg laid smaller eggs; egg-laying ceased irreversibly after 6 weeks at the highest dose (10).

Mutagenicity and related end-points

EDB induced sister chromatid exchange, mutations, and unscheduled DNA synthesis in both human and rodent cells in vivo. In rodents, DNA strand breaks were found in vitro and in vivo (11).

Carcinogenicity

EDB has been demonstrated to be carcinogenic in rodents after administration by all three routes of exposure. It was administered by gavage in corn oil 5 times per week to Osborne-Mendel rats (50 per sex per dose for the test compound, 20 per sex per dose for controls) at time-weighted average doses of 38 or 41 mg/kg of body weight per day to males and 37 or 39 mg/kg of body weight per day to females. Because of high toxicity and premature deaths during the course of the study, the high dose was readjusted and the study was terminated early, after 49 weeks for males and 61 weeks for females. Early developing squamous cell carcinoma of the forestomach, a contact-site cancer preceded by tissue damage, was observed in both sexes; incidences were 0/20, 45/50, and 33/50 in males and 0/20, 40/50, and 29/50 in females. Liver cancers were observed in females, and haemangiosarcomas of the spleen, a relatively rare tumour at a site remote from the site of administration, were seen in males at incidences of 0/20, 11/50, and 4/50 in controls, low-, and high-dose groups, respectively (8).

A similar protocol was followed with B6C3F1 mice given 0, 62, or 107 mg/kg of body weight per day (time-weighted average doses) for 78 weeks, except for low-dose females, in which the study was terminated at 90 weeks. EDB produced squamous cell carcinomas of the forestomach and alveolar/bronchiolar lung tumours in both sexes (8).

In long-term inhalation studies in mice and rats, EDB produced adenomas and carcinomas of the nasal cavity, haemangiosarcomas of the spleen, and mammary tumours in both species. An increased incidence of tunica vaginalis mesotheliomas in male rats and lung tumours in both sexes of mice was also observed (9). EDB also induced skin and lung tumours in mice after skin application (12).

15.16.6 Effects on humans

One lethal case of poisoning has been reported in an adult female who ingested 65 mg of EDB per kg of body weight (6). Prolonged contact with EDB has caused skin irritation (13). Long-term occupational exposure affects semen quality. Statistically significant decreases in sperm count, the percentage of viable and motile sperm, and increases in the proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) were observed among exposed men as compared with controls (3). No sister chromatid exchanges have been seen in humans occupationally exposed during spraying and fruit packing (11).

In 1987, IARC found the evidence for carcinogenicity to humans to be inadequate (14), on the basis of three studies. The first study looked at the mortality of 161 men exposed to EDB in two factories since the mid-1920s and 1942, respectively. By 1 January 1976, 36 workers had died, seven of them from cancer (5.8 expected) (15). In the second study, the mortality of 2510 male workers employed at a chemical plant was investigated. EDB was one of several chemicals used and was apparently a minor component of the mixed exposure. No statistically significant excess of cancer was found at any site (16). Finally an excess of lymphoma was detected in a mortality study of grain workers in the USA who might have been exposed
to EDB, among other compounds (17).

15.16.7 Conclusions

In 1987, IARC concluded that the evidence for carcinogenicity to humans was inadequate but that the animal data were sufficient to establish carcinogenicity, assigning EDB to Group 2A (14). EDB has been found to be genotoxic in both in vitro and in vivo assays.

Although EDB appears to be a genotoxic carcinogen, the studies to date are inadequate for mathematical risk extrapolation. Therefore, a guideline value for EDB has not been derived. EDB should be re-evaluated as soon as new data become available.

References


15.17 Heptachlor and heptachlor epoxide

15.17.1. General description

**Identity**

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS no.</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heptachlor</td>
<td>76-44-8</td>
<td>C_{10}H_{5}Cl_{7}</td>
</tr>
<tr>
<td>Heptachlor epoxide</td>
<td>1024-57-3</td>
<td>C_{10}H_{5}Cl_{7}O</td>
</tr>
</tbody>
</table>

Heptachlor is the common name for 1,4,5,6,7,8,8-heptachlor-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene. Heptachlor epoxide is the common name for 2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-2,5-methano-2H-indene(1,2b)oxirene (1).

**Physicochemical properties (1-7)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Heptachlor</th>
<th>Heptachlor epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point (°C)</td>
<td>93</td>
<td>160-161.5</td>
</tr>
<tr>
<td>(99.5% pure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.57-1.59</td>
<td>-</td>
</tr>
<tr>
<td>Vapour pressure at 25 °C (kPa)</td>
<td>53 × 10^{-6}</td>
<td>53 × 10^{-6}</td>
</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>3.87-5.44</td>
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</tr>
<tr>
<td>Water solubility at 25 °C (mg/litre)</td>
<td>0.056</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Organoleptic properties**

Pure heptachlor is a white crystalline solid with a camphor-like odour.

**Major uses**

Heptachlor is applied as a soil treatment, a seed treatment (maize, small grains, and sorghum), or directly to foliage. It is used to control ants, cutworms, maggots, termites, thrips, weevils, wireworms, and many other insect pests in both cultivated and uncultivated soils. Heptachlor also controls household insects and pests of humans and domestic animals (5). In many countries, heptachlor is banned or applied only by subsurface injection.

Heptachlor epoxide is not commercially available but is an oxidation product of heptachlor (1).

**Environmental fate**
Heptachlor is moderately persistent in soil, where it is mainly transformed into its epoxide. It may undergo significant photolysis, oxidation, and volatilization (6,8,9). It binds to soil particles and migrates slowly (10). The soil half-life of heptachlor under certain conditions may be as long as 2 years (11). Heptachlor epoxide is very resistant to further chemical or biological changes in soil. It binds to soil particles and migrates slowly (10). Its half-life in various soils has been reported to be as long as several years (12).

Photolysis, oxidation, hydrolysis, and biotic reactions do not appear to be important processes in reducing heptachlor epoxide levels in aquatic media (6,8), whereas volatilization seems to be significant (13).

15.17.2. Analytical methods

Heptachlor may be determined in water samples by a liquid-liquid extraction followed by gas chromatography. Detection and measurement may be accomplished by electron-capture or electrolytic conductivity gas chromatography. The sensitivity of the method is 1-10 ng/litre (14).

15.17.3. Environmental levels and human exposure

Air

In a survey carried out in the USA in 1971, heptachlor was found in samples from two of nine cities at a maximum level of 19.2 ng/m³ (15). In air samples taken from 1972 to 1974 in a cotton-growing area of the USA, the maximum heptachlor level was 0.8 ng/m³ (16).

Water

Heptachlor and heptachlor epoxide have been found in drinking-water at ng per litre levels (17-19). Heptachlor epoxide has been found in drinking-water, groundwater, land run-off, and river water at seven locations in the USA and Europe and in sediments, lakes, rivers, tapwater, and effluent from a biological sewage treatment plant at 28 such locations (19,20).

Food

Heptachlor and heptachlor epoxide have been found in many food classes (21,22). Human milk can be contaminated with heptachlor epoxide (23). Based on a total diet study conducted by the US Food and Drug Administration, estimated daily intakes of heptachlor and heptachlor epoxide for men aged 25-30 were 0.007 µg and 0.184 µg, respectively (24).

Estimated total exposure and relative contribution of drinking-water

Diet is likely to be the greatest source of exposure to heptachlor epoxide.

15.17.4. Kinetics and metabolism in laboratory animals and humans

Heptachlor is rapidly absorbed from the gastrointestinal tract of rats following intragastric administration (25). Heptachlor epoxide is distributed throughout the body of rats and dogs (25,26). Heptachlor is metabolized by rats to heptachlor epoxide, 1-hydroxychlorde, and 1-hydroxy-2,3-epoxychlorde, which are the major faecal metabolites. In vitro studies have shown that heptachlor epoxide formation is greater in rats than in humans, and that metabolism is, in general, comparable in the two species. Faeces represent the major route of heptachlor elimination by rats (27).
15.17.5. Effects on laboratory animals and in vitro test systems

**Acute exposure**

In the rat, mouse, rabbit, guinea-pig, hamster, and chicken, oral LD$_{50}$s for heptachlor range from 40 to 260 mg/kg of body weight (28).

**Short-term exposure**

Evidence of significant liver damage and altered liver function was reported in rats maintained on diets containing heptachlor at 7-12 mg/kg of body weight per day for up to 14 days and 1 mg/kg of body weight per day for 5-7 days (29,30).

**Long-term exposure**

Male and female rats were fed diets containing heptachlor epoxide at 0, 5, 10, 20, 40, 80, 160, or 300 mg/kg for 2 years. Concentrations of 80 mg/kg or higher resulted in 100% mortality in 2-20 weeks. At 40 mg/kg, all the females died within 54 weeks, but there was no effect on male mortality up to 104 weeks. Diets containing 20 mg/kg or less did not produce any sign of illness in male or female rats, but an increase in liver weight was observed in male rats dosed with more than 10 mg/kg and females given 5 mg/kg (31).

Diets containing 0, 0.5, 2.5, 5.0, or 7.5 mg of heptachlor epoxide per kg were given to groups of five dogs for 60 weeks. No deaths attributed to heptachlor epoxide occurred. The weights of the male dogs increased in inverse proportion to the concentration of the compound in the diet, whereas those of the females were normal. Liver weights increased at 5.0 mg/kg and above. Degenerative liver changes were seen in only one dog at 7.5 mg/kg. From this study, a NOAEL of 2.5 mg/kg of diet, equivalent to 0.06 mg/kg of body weight per day, can be derived (31).

In a 2-year study, dogs fed heptachlor epoxide in the diet at concentrations of 0, 1, 3, 5, 7, or 10 mg/kg exhibited an increase in liver weight at the highest concentration and an increase in the incidence of histopathological changes in the liver (enlargement and vacuolation of centrilobular or scattered hepatocytes) at all but the lowest concentration. Similar histopathological changes persisted during 6 months of the recovery period. The NOAEL was 1 mg/kg of diet, equivalent to 0.025 mg/kg of body weight per day (32).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

According to a poorly documented multigenerational study in rats fed heptachlor, litter size and viability were reduced and cataracts occurred in pups (33). No indications of teratogenicity have been found in rats, rabbits, chickens, or beagle dogs exposed to heptachlor (28). Rats fed 19.5 mg of heptachlor per kg of diet for 90 days showed a decrease in androgen receptor sites, nucleic acids, and proteins in the ventral prostate (34).

Fertility was inhibited in female mice by three heptachlor injections of 25 mg/kg of body weight given at a rate of one per week. There was also an increase in estrogen metabolism and a decrease in the uterotrophic activity of estrogen. Inhibition of the response of rat uterus to estrogen was seen; the LOAEL was 5 mg/kg of body weight for 7 days (35).

In a two-generation reproduction study in dogs fed heptachlor epoxide in the diet at concentrations of 1, 3, 5, 7, or 10 mg/kg, there was an increase in the mortality of F$_2$ pups at all but the lowest concentration. The NOAEL based on this finding was 1 mg/kg, equivalent to 0.025 mg/kg of body weight per day (32).

**Mutagenicity and related end-points**
Heptachlor did not induce dominant lethal mutations in mice. In one study, it induced unscheduled DNA synthesis in human fibroblast cultures but not repair synthesis in cultured rodent cells. It inhibited intercellular communication in rodent cell systems but was not mutagenic in cultured rat liver cells. It did not induce sex-linked recessive mutations in Drosophila or gene conversion in yeast. It was mutagenic in plants but not in bacteria. In one study, positive results were reported for technical-grade but not commercial-grade heptachlor. It did not produce plasmid DNA breakage (36).

Carcinogenicity

Heptachlor containing about 20% chlordane produced neoplasms in mice following oral administration; the results of studies on rats were inconclusive. Oral administration of heptachlor increased the incidence of liver tumours induced in mice by the oral administration of N-nitrosodiethylamine (36).

15.17.6. Effects on humans

Clinical case-studies of acute exposure (via ingestion, or the dermal or inhalation routes) to chlordane-containing heptachlor document a pattern of central nervous system effects similar to that found in animals (e.g. irritability, salivation, laboured respiration, muscle tremors, convulsions) (37,38). Heptachlor does not appear to be carcinogenic in humans (39-42).

15.17.7. Guideline value

IARC reviewed the data on heptachlor in 1991 and concluded that the evidence for carcinogenicity was sufficient in animals and inadequate in humans, classifying it in Group 2B (43).

JMPR has evaluated heptachlor on several occasions and in 1991 established an ADI of 0.1 µg/kg of body weight on the basis of a NOAEL of 0.025 mg/kg of body weight per day from two studies in the dog, incorporating an uncertainty factor of 200 (100 for inter- and intraspecies variation and 2 for the inadequacy of the database) (32). With an allocation of 1% of the ADI to drinking-water, because the main source of exposure seems to be food, a guideline value is 0.03 µg/litre.

References


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31. Witherup S, Cleveland FP, Stemmer K. The physiological effects of the introduction of heptachlor epoxide in varying levels of concentration into the diet of CFN rats. Cincinnati, OH, Kettering Laboratory, University of Cincinnati, 1959 (unpublished report submitted to WHO by Velsicol Chemical Corp., Rosemont, IL, USA).


15.18 Hexachlorobenzene

15.18.1. General description

**Identity**

CAS no.: 118-74-1  
Molecular formula: C₆Cl₆

**Physicochemical properties (1-4)**

<table>
<thead>
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<th>Value</th>
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<td>Boiling point</td>
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<td>Vapour pressure</td>
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</tbody>
</table>

**Major uses**

Hexachlorobenzene (HCB) is a selective fungicide used to control dwarf bunt of wheat, a soil- and seed-borne disease caused by *Tilletia controversa*. In many countries, its production and use as a fungicide have ceased. At present, its main importance appears to be as a by-product of several chemical processes or an impurity in some pesticides (2,5).

**Environmental fate**

HCB is a widespread contaminant. It photolyses slowly in the atmosphere, where it has a half-life of about 80 days (6). It has very low solubility in water but, despite its relatively low vapour pressure, volatilizes from water at a significant rate (4,7). The main chemical reaction in water is slow photolysis, whereas hydrolysis and oxidation appear to be unimportant (6). Biotransformation of HCB in surface water, sludge, or soil suspensions is extremely low: <0.1% is converted into carbon dioxide in 5-7 days (8). HCB is strongly adsorbed by soil and sediments. Because of its resistance to abiotic and biotic degradation and very high octanol-water partition coefficient, it can bioaccumulate in aquatic organisms (9).

15.18.2. Analytical methods

HCB in water can be extracted with hexane and then determined by gas chromatography using an electron-capture detector. The detection limit of this method is 5 ng/litre (10).
15.18.3. Environmental levels and human exposure

**Air**

Atmospheric concentrations of HCB have rarely been measured and are hardly quantifiable. Levels of 1-24 and 0.1 µg/m³ have been reported in the USA and Scandinavia, respectively (11,12).

**Water**

HCB was not found (detection limit of 0.1 µg/litre) in 104 surface waters and 12 groundwater supplies examined in the USA in 1984 (13). From 1970 to 1983, HCB concentrations of up to 0.12 µg/litre were present in the Rhine; after 1983, they decreased significantly. Concentrations in sediments were about 1000 times higher than those in the corresponding surface waters (14).

**Food**

HCB can be taken up by crops if used as a fungicide or if present as a soil contaminant. Carrots show a particular affinity for HCB (14). In agricultural areas of the former Czechoslovakia, HCB was found at nearly all links in the food-chain in 1975-1983; the highest levels were found in wheat, milk fat from cows, and human milk (15). It has been found in many fish taken from surface waters; levels higher than 0.3 mg/kg have been found in fish from the river Rhine (16). Freshwater fish contain more HCB than saltwater fish (17).

**Estimated total exposure and relative contribution of drinking-water**

Diet is probably the major route of exposure to HCB (13), through fish contaminated by industrial emissions, animal products contaminated by HCB-treated animal feed, and crops contaminated by soils and pesticides (14). In the Netherlands in 1978, daily HCB intake was in the range <1-12 µg; the median was 1 µg (14). The estimated dietary intake in the USA was 2 µg/kg of body weight per day in 1981-1982 (18).

15.18.4. Kinetics and metabolism in laboratory animals and humans

More HCB is absorbed when administered in olive oil than as an aqueous suspension or the solid crystalline form (80% v. 20%) (19). Following administration to male rats, the highest concentrations were detected in adipose tissue, bone marrow, skin, the Harderian gland, nasal mucosa, and the preputial gland (20).

HCB is metabolized slowly to give lower chlorinated benzenes, chlorinated phenols, and other lower metabolites; glucuronide and glutathione conjugates have been also detected (21). Most is excreted in faeces as the parent compound, a small fraction, about 5%, being excreted in the urine as polar metabolites (22). Lactation is an effective method of HCB elimination for the cow and mouse but not for humans (23).

15.18.5. Effects on laboratory animals and in vitro test systems

**Acute exposure**

LD₅₀s varying from less than 1000 to over 10 000 mg/kg of body weight have been reported for different animal species. The symptoms observed were convulsions, tremors, weakness, ataxia, paralysis, and pathological changes in organs (24).
Short-term exposure

HCB was fed in the diets to Swiss mice (0, 100, or 200 mg/kg), Sprague-Dawley rats, and Syrian golden hamsters (0, 200, or 400 mg/kg) for 90 days. It induced severe hyperplasia of lymphohaematopoietic centres, with frequent lymphocytic infiltrations into the liver and kidneys, as well as severe haemosiderosis in the spleen and liver. Toxic liver lesions, including several degenerations, peliosis, necroses leading to toxic hepatitis, and cirrhosis that developed into neoplastic growths, were most severe in male hamsters and rats but were seldom seen in mice. The kidneys were also affected, showing toxic tubular nephrosis and nephritis (25).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a four-generation test with Sprague-Dawley rats, the NOAEL was 20 mg/kg in the diet (26). Some teratogenic effects of HCB were observed in Wistar rats at doses of up to 120 mg/kg of body weight administered during organogenesis, but could not be reproduced (27). HCB was found to cause developmental effects in fetal CD-1 mice whose mothers ingested 100 mg/kg of body weight per day on days 7-16 of gestation (28). HCB did not exhibit developmental effects in New Zealand rabbits (29).

Mutagenicity and related end-points

HCB was not found to be mutagenic in five strains of Salmonella typhimurium, with or without metabolic activation (30). It was negative in dominant lethal mutation studies with rats (27), but was shown to be mutagenic in Saccharomyces cerevisiae (31). HCB gave negative results in the Ames test and sister chromatid exchange (32).

Carcinogenicity

Groups of Swiss mice were fed diets containing HCB (>99.5% pure) at 0, 50, 100, or 200 mg/kg. Liver cell tumours were found in the two highest dose groups but not in controls or in the group receiving 50 mg/kg (33). In Syrian golden hamsters fed diets containing HCB (99.5% pure) at 0, 50, 100, or 200 mg/kg throughout their life, hepatomas, liver haemangioendotheliomas, and thyroid adenomas developed in both sexes (34).

Sprague-Dawley rats were fed diets containing 0, 75, or 150 mg of HCB per kg for 2 years (25). Hepatomas, bile duct adenomas, and hepatocellular carcinomas were seen in very high incidences in female rats; renal adenomas were observed in male rats.

In a two-generation feeding study in Sprague-Dawley rats, increased incidences of parathyroid adenomas and adrenal phaeochromocytomas were observed in animals of both sexes, and neoplastic nodules in females of the F₁ generation (35). HCB also induced liver neoplastic nodules and hepatocellular carcinomas in F334 rats, females yielding many more tumours than males (36).

15.18.6. Effects on humans

IARC has found the evidence for carcinogenicity of HCB in humans to be inadequate, as no report of a direct association between HCB and human cancer is available. Hepatocellular carcinoma has been associated with porphyria; however, although abnormal porphyrin metabolism persisted at least 20 years after an epidemic of porphyria cutanea tarda in Turkey, caused by the consumption of grain treated with HCB, no excess cancer occurrence was reported in this population 25 years after the accident (37).

15.18.7. Guideline value

IARC has evaluated the evidence for carcinogenicity of HCB in animals and humans and assigned it to Group 2B (37). Because HCB has been shown to induce tumours in three animal species and at a variety
of sites, a linearized low-dose extrapolation model was used to calculate concentrations in drinking-water associated with excess lifetime cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$. On the basis of liver tumours observed in female rats in a 2-year dietary study (25) and applying the linearized multistage model, concentrations of 10, 1, and 0.1 µg/litre in drinking-water correspond to excess lifetime cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$, respectively.

References


11. Landuer L, Skoglund PO. *Hexachlorobenzenen (HCB), oktaklorstyren (OCS) och hexaklorcyclohexan-lindan i vattenmiljö. [Hexachlorobenzene (HCB), octachlorostyrene (OCS) and hexachlorocyclohexane-lindane in the water environment.]* Stockholm, Swedish Environmental Protection Board, 1978 (NL Publication No. 13401).


15.19 Isoproturon

### 15.19.1. General description

**Identity**

CAS no.: 34123-59-6  
Molecular formula: C₁₂H₁₈N₂O

The IUPAC name for isoproturon is 3-(4-isopropylphenyl)-1,1-dimethylurea or 3-ₚ-cumenyl-1,1-dimethylurea.

**Physicochemical properties (1)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
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<tbody>
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<td>Physical state</td>
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<td>155-156 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>0.003 × 10⁻³ Pa at 20 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>72 mg/litre at 20 °C</td>
</tr>
</tbody>
</table>

**Organoleptic properties**

No odour was detected at a concentration of 8.0 mg/litre (99% purity, dissolved in still, bottled water, equilibrated to 40 °C, eight assessors) (Water Research Centre, unpublished data, 1990).
**Major uses**

Isoproturon is a selective, systemic herbicide used in the control of annual grasses and broad-leaved weeds in cereals (1,2).

**Environmental fate**

Isoproturon is mobile in soil and has been detected in both surface water and groundwater. In water, it is quite persistent and hydrolyses slowly; the half-life is about 30 days (3). In soil, isoproturon undergoes enzymatic and microbial demethylation at the urea nitrogen and hydrolysis of the phenylurea to form 4-(2-hydroxyisopropyl)aniline. It also undergoes some photochemical degradation; photometabolites identified include 3-(4-isopropylphenyl)-1-methylurea, 3-(4-isopropylphenyl)urea, 4,4’-diisopropylazobenzene, and 4,4’-diisopropylazoxybenzene. Under field conditions, its half-life is about 40 days in temperate climates and 15 days in tropical climates (4).

15.19.2. Analytical methods

Isoproturon may be determined by separation by reverse-phase high-performance liquid chromatography followed by ultraviolet or electrochemical detection. High levels of phenoxyacidic herbicides may interfere with the determination (5). Detection limits between 10 and 100 ng/litre have been reported (6,7).

15.19.3. Environmental levels and human exposure

**Air**

Because of isoproturon’s low vapour pressure and short half-life in soil, it is unlikely that there is significant human exposure from air.

**Water**

Raw waters may become contaminated with isoproturon from production plant discharges and diffuse agricultural sources. In Germany, concentrations of between 0.1 and 0.125 µg/litre have been recorded in surface water (8). In groundwater, it has been detected at concentrations of between 0.05 and 0.1 µg/litre (8,9). Levels above 0.1 µg/litre have occasionally been detected in drinking-water (3).

**Food**

It is generally considered that diet is not a major source of exposure to isoproturon for the general population. No measurable residues of isoproturon or any metabolites containing the isopropylaniline moiety were detected in grain samples, where the detection limit ranged from 0.1 to 0.01 mg/kg (10).

**Estimated total exposure and relative contribution of drinking-water**

The data on environmental levels of isoproturon are limited. However, results suggest that exposure of the general population to this compound is not significant.

15.19.4. Kinetics and metabolism in laboratory animals and humans

Isoproturon is readily and rapidly absorbed when given orally. Distribution is rapid, and no accumulation of isoproturon in any particular organ or tissue has been reported (11). It is rapidly metabolized by the rat, the major routes being N-demethylation and oxidation of the N-methyl groups and isopropyl moiety followed by conjugation reactions. The N-hydroxymethyl derivative of substituted urea has not been detected, although this compound may be formed at a low concentration as a short-term intermediate. In the rat, isoproturon metabolites are rapidly excreted in the urine (10,11).
15.19.5. Effects on laboratory animals and *in vitro* test systems

**Acute exposure**

Isoproturon is of low acute oral toxicity in mammals, although the LD$_{50}$ varies considerably according to the vehicle used (11). Oral LD$_{50}$s range from 1826 to 3600 mg/kg of body weight for a number of species (11,12). It does not cause skin and eye irritation or sensitization after repeated dermal exposure (11).

**Short-term exposure**

In a 90-day dietary study in rats, animals receiving 400 mg/kg and higher showed a dose-dependent and reversible increase in liver weight, proliferation of the smooth endoplasmic reticulum in hepatocytes, and induction of several hepatic enzymes. Reversible haemolytic anaemia was also observed at 2000 mg/kg. The NOAEL was 80 mg/kg, equal to a daily dose of 7 mg/kg of body weight (11).

In a 90-day study, beagle dogs fed isoproturon at dose levels of 0, 50, 100, or 500 (which was increased to 800) mg/kg of diet showed a dose-dependent increase in liver weight. Toxic haemolytic anaemia and Heinz body formation were seen at the highest dose. Haematological abnormalities were also present in the 100 mg/kg group. The NOAEL for this study was 50 mg/kg, equivalent to a daily intake of 3.2 mg/kg of body weight (11).

Liver damage was not observed in a 30-day dietary study in mice, suggesting that isoproturon metabolism may be different in this species. The NOAEL was 2000 mg/kg, equal to a daily intake of 307 and 378 mg/kg of body weight in male and female mice, respectively (11).

**Long-term exposure**

Rats (80 per sex per dose, species not specified) were given isoproturon in the daily diet at concentrations of 0, 80, 400, or 2000 mg/kg for 104 or 115 weeks. At the highest dose, serum enzyme activities and cholesterol values were increased, indicative of hepatic enzyme induction. At the two highest doses, there was a marginal reduction of all red blood cell parameters, liver weights were increased, and acidophilic foci (areas of hepatocellular change) were noted on histopathological examination. The NOAEL was 80 mg/kg, equal to a daily intake of 3.1 and 3.8 mg/kg of body weight in males and females, respectively (11).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Isoproturon was not teratogenic in rats or rabbits administered doses up to 25 or 100 mg/kg of body weight per day by gavage, respectively. In a two-generation study, rats were fed isoproturon at concentrations of 0, 80, 400, or 2000 mg/kg of diet per day. Marked indications of toxicity to the parents and pups were observed at the highest dose. Litter sizes and numbers of implantations were reduced as a result of maternal toxicity. A slight inhibition of body weight gain was also found in the group receiving 400 mg/kg of diet. No effects on reproduction, fertility, or sexual maturation were reported, and a NOAEL of 80 mg/kg of diet was identified (11).

**Mutagenicity and related end-points**

Isoproturon has been tested in a number of *in vitro* and *in vivo* short-term assays for mutagenicity. The majority of the evidence, particularly in recent years, indicates that it is not mutagenic in bacterial, eukaryotic, or *in vitro* and *in vivo* mammalian test systems (11).

**Carcinogenicity**

In a 2-year study in CD-1 mice, no evidence was found to show that isoproturon was carcinogenic (11). In
addition, no evidence of hepatic enzyme induction or increased liver weights was seen. In a 2-year dietary study in Sprague-Dawley rats, isoproturon caused an increase in hepatocellular tumours, but only at doses that also caused liver toxicity. No liver toxicity was apparent at 80 mg/kg of diet, nor was there an increase in the incidence of tumours. From these studies, it appears that isoproturon may be a tumour promoter (11).

This was confirmed in a promoter study in male rats in which animals were pretreated with nitrosodiethylamine (NDEA) for 14 days followed by a treatment-free week. One group of animals was subsequently treated for 31 weeks with isoproturon and another group with NDEA only. In isoproturon-treated animals, there was a marked increase in the incidence of preneoplastic and neoplastic lesions in the liver as compared with the NDEA-treated group (11).

15.19.6. Effects on humans

Isoproturon has been in commercial use for a relatively short period, and so far no cases of human poisoning have been reported. Data on human health effects are limited to studies involving occupational exposures. One 3-year study was carried out on a group of workers employed in various parts of the manufacturing process. Urine and blood analysis failed to show any pathological abnormalities in the peripheral blood count or any indication of haemolytic anaemia (11).

15.19.7. Guideline value

The NOAELS in a 90-day study in dogs and a 2-year feeding study in rats were approximately 3 mg/kg of body weight per day (11). A TDI of 3 µg/kg of body weight can be calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 because there is evidence of non-genotoxic carcinogenicity in rats). With an allocation of 10% of the TDI to drinking-water, a guideline value of 9 µg/litre was calculated.

References


15.20 Lindane

15.20.1. General description

**Identity**

CAS no.: 58-89-9  
Molecular formula: $\text{C}_6\text{H}_6\text{Cl}_6$

In the production of hexachlorocyclohexane, a mixture of isomers is formed, consisting mainly of the $\alpha$-, $\beta$-, and $\gamma$-isomers. Lindane is the name given to 99% pure $\gamma$-hexachlorocyclohexane ($\gamma$-HCH).

**Physicochemical properties of $\gamma$-HCH (1-3)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>112.8 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>288 °C</td>
</tr>
<tr>
<td>Density</td>
<td>1.85 g/cm$^3$ at 20 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>7-17 mg/litre at 20 °C</td>
</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>3.2-3.7</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>$0.434 \times 10^{-2}$ Pa at 20 °C</td>
</tr>
</tbody>
</table>

**Organoleptic properties**

Odour thresholds of 12 mg/litre for lindane and 0.3 µg/litre for $\beta$-HCH have been reported (2).

**Major uses**

Lindane is used as an insecticide on fruit and vegetable crops (including greenhouse vegetables and tobacco), for seed treatment, and in forestry. It is also used as a therapeutic pesticide (e.g. in the treatment of scabies) in humans and animals (1,2). Several countries have restricted the use of lindane.

**Environmental fate**

In soil, lindane can be degraded under aerobic conditions; the half-life ranges from 88 to 1146 days. $\gamma$-Pentachlorocyclohexene, hexa-, penta-, tetra-, and trichlorobenzenes, and penta- and tetrachlorophenols are the degradation products most commonly found. Anaerobic degradation is more rapid than aerobic degradation under laboratory conditions (half-life 12-174 days). Under anaerobic conditions, the same chlorinated benzenes and hexenes are found, but not the phenols. Leaching of lindane to groundwater rarely occurs. In surface waters, it can be removed by evaporation. Ultraviolet light seems to transform $\gamma$-HCH into $\alpha$-HCH to some extent. Bacteria also influence the isomerization of $\gamma$-HCH to $\alpha$-HCH. The
degradation products found in soils have also been found in water (1,3).

15.20.2. Analytical methods

Lindane in water can be determined by extraction with petroleum ether followed by gas chromatography. The limit of detection is 0.01 µg/litre (1).

15.20.3. Environmental levels and human exposure

Air

Background levels of lindane in the range 0.01-0.7 ng/m³ have been found in “unpolluted” remote areas, whereas levels in urban and agricultural areas range from 0.1 to 2 ng/m³ (2-4). α-HCH is present together with γ-HCH, often in higher concentrations (1,3,4). In indoor air, levels range from 6 ng/m³ (average for homes built on waste dumps) to 40-60 µg/m³ after treatment for insect control (1,3). Lindane can also be present in cigarette smoke (2).

Water

Lindane enters water from direct application for the control of mosquitoes, from use in agriculture and forestry, from precipitation and, to a lesser extent, from occasional contamination of wastewater from manufacturing plants. Normal levels in precipitation are 0.4-155 ng/litre, but levels up to 43 µg/litre have been measured in India (4).

In surface waters, levels of 0.01-0.1 µg/litre have been reported (1-3). Particularly high concentrations, up to 12 µg/litre, are found in wastewater-contaminated rivers (4). Concentrations in groundwaters have been reported to range from 3 to 163 ng/litre (2,4).

Food

HCH isomers are found in dairy products, meat, fish, poultry, garden fruits, oils and fats, leafy and root vegetables, and sugar. Spices and herbs contain the highest levels of α- and β-HCH, whereas pork and beef fat contain the highest levels of γ-HCH (up to 3200 and 1700 µg/kg of fat, respectively). Most animal fats and eggs contain less than 10 µg of γ-HCH per kg (1,3). Breast milk contains γ- and occasionally γ-HCH at mean levels of 3 and 6 µg/kg of milk, respectively (2,5).

Estimated total exposure and relative contribution of drinking-water

Daily intake of HCH isomers in adult diets in the USA in 1981-82 was reported to be 10 ng/kg of body weight for total HCH (8 ng of α-HCH and 2 ng of γ-HCH per kg of body weight) (2). In the Netherlands, the daily intake from food has been calculated to be 1 µg for the α-, β-, and γ-isomers, or approximately 15 ng/kg of body weight (1,3). Intake from air may be considerable for people living in houses treated for pest-control purposes.

15.20.4. Kinetics and metabolism in laboratory animals and humans

After oral administration of lindane, absorption is almost complete. Dermal absorption also appears to be considerable. Absorption is enhanced in the presence of lipids. In rats, lindane is stored in fat to some extent, but elimination via urine is fairly rapid. In cattle, γ-HCH levels were found to be 10 times higher in adipose tissues than in feed (2).

In humans, γ-HCH content seems to increase with age, but is not correlated with levels or duration of exposure. Higher levels of the β-isomer are found in over 80% of postmortem human adipose tissue
samples (2). Lindane crosses the placenta and can also be present in human milk (2,3).

In general, lindane in animals and humans is metabolized via dehydrochlorination, dechlorination, dehydrogenation, and oxidation, yielding hexachlorocyclohexene, pentachlorocyclohexene, tetrachlorocyclohexene, and hexachlorocyclohexenol, respectively, as intermediates. The final metabolites are isomers of dichlorophenol, trichlorophenol, and tetrachlorophenol (6).

15.20.5. Effects on laboratory animals and in vitro test systems

Acute exposure

The oral LD$_{50}$s of $\gamma$-HCH in mice and rats ranged from 70 to 480 and from 90 to 300 mg/kg of body weight, respectively. Dermal LD$_{50}$s in rats and rabbits ranged from 50 to 500 mg/kg of body weight. An inhalation test in rats gave an LC$_{50}$ of 1600 mg/m$^3$ (2).

Neurotoxic effects have been reported in several species of animals. Convulsions and seizures were reported following a single intragastric dose of approximately 60-150 mg/kg of body weight in rats, and avoidance response latency was statistically increased in rats given a single dose of 15 mg/kg of body weight by gavage (2).

Short-term exposure

Two 90-day studies in rats showed the same type of effects in liver and kidneys. Effects in kidneys were found only in males. In the first study, in which doses of 0.2, 0.8, 4, 20, or 100 mg/kg of feed were administered, the two highest dose levels resulted in liver enlargement, signs of liver enzyme induction, hypertrophy of the liver, renal tubular changes, and hyaline droplets in the kidneys. The dose level of 4 mg/kg, equal to 0.3 mg/kg of body weight per day, was considered as the NOAEL (1,7).

In the second study (dose levels of 2, 10, 50, or 250 mg/kg in the diet), liver effects and kidney changes occurred at 10 mg/kg and higher, but not at 2 mg/kg (8). Because the effects at 10 mg/kg were minimal, this dose level was chosen by JMPR as the NOAEL in 1989 (9), to be used as the basis for the ADI. However, the reviewer of the study calculated the compound intake as 0.75 mg/kg of body weight on the basis of the food intake, which were measured only in weeks 1, 2, 3, 6, 9, and 13. This calculation is considered inappropriate, because food intake was measured only approximately as an indicator of toxicity and for the calculation of food efficiency, to determine whether any effect on body weight might have been caused by a decrease in food intake. Therefore, use of the normal factor of 20 for conversion of mg/kg in food to mg/kg of body weight per day is considered more appropriate. The NOAEL then becomes equivalent to 0.5 mg/kg of body weight per day.

Long-term exposure

Beagle dogs (4 per sex per dose) were fed lindane in the diet at 0, 25, 50, or 100 mg/kg for 2 years. At 100 mg/kg, SAP activity was slightly increased and somewhat darker coloration and a friable consistency of the liver were observed. Liver function tests (BSP retention) showed no functional disturbance, and histological examination showed no morphological irregularity corresponding to the gross observations (10). The NOAEL, based on gross morphological changes in the liver and SAP elevations, was 50 mg/kg, which corresponds to 1.6 mg/kg of body weight per day, based on actual food consumption data (1,9).

Reproductive toxicity, embryotoxicity, and teratogenicity

No teratogenic effects of $\gamma$-HCH were observed in studies on mice, rats, rabbits, or hamsters; embryotoxicity (at maternally toxic doses) was observed in rats only (6,11). In several reproduction studies on rats and in one study on rabbits, reproductive parameters were not affected. A marginal effect on liver
weight was seen in a rat study at 25 mg/kg of feed, the lowest dose tested (1,6,11).

In a 13-week study on β-HCH in rats, pup viability was decreased at 0.5 mg/kg of body weight per day. In the dams, dose-related changes in ovaries and uterus epithelium were noticed even at the lowest dose tested (0.1 mg/kg of body weight per day) (12).

**Mutagenicity and related end-points**

The mutagenic activity of lindane was examined in plants, bacteria, yeast, *Drosophila*, and mammalian and human cells *in vitro* as well as in live mammals. Lindane did not induce mutations in any of the systems examined; some cytogenetic damage, however, was observed in mammalian and human cells *in vitro*. Mitotic disturbances, polyploidy, and chromosomal aberrations have been observed (6).

**Carcinogenicity**

α-HCH or γ-HCH administered in the diet to rats was not carcinogenic. Mice sometimes developed liver tumours when exposed to high doses of γ-HCH, whereas they always did so when fed high doses of α-HCH (6).

15.20.6. Effects on humans

Deaths of humans (usually children) have been reported following ingestion of lindane. A single dose of 840 mg/kg of body weight in adults and 180 mg/kg of body weight in children was lethal (11). An 18-h whole-body dermal application of 1% lindane lotion to a 2-month-old baby for the treatment of scabies resulted in death. γ-HCH concentrations of 110 and 33 µg/kg were found in the brain and heart blood, respectively (13).

The most commonly reported effects associated with oral or occupational exposure to β-HCH are neurophysiological and neuropsychological disorders and gastrointestinal disturbances. In an occupational study on the neurological effects of HCH, no pathological signs or sensibilities were recorded (14). Total HCH levels found in serum were 10-72 µg/litre.

In a study conducted in an Indian pesticide factory, serum levels in handlers directly exposed to HCH for 7-30 years were 195-1152 µg/litre, in non-handlers exposed to HCH in air and dust 83-656 µg/litre, and in the control group (employed in the factory but not in contact with HCH) 0-370 µg/litre. Most of the HCH in the serum was in the form of β-HCH (70%), followed by α-HCH and γ-HCH. The main effects seen were paraesthesia of the face and extremities (94% of handlers and 69% of non-handlers). Headache and giddiness occurred in over 70% of the handlers and in about 40% of the non-handlers, as compared with 7% of the control group (15).

15.20.7. Guideline value

Lindane causes liver tumours in mice given very high doses, but there is evidence that this is a result of tumour promotion. In 1987, IARC classified lindane in Group 2B (16). Moreover, in 1989, after reviewing all available *in vitro* and *in vivo* short-term tests, JMPR concluded that there was no evidence of genotoxicity and established an ADI of 8 µg/kg of body weight based on liver and kidney toxicity observed in a short-term study in the rat (9).

On the basis of the same study, but using a compound intake estimate considered to be more appropriate in the light of additional data, a TDI of 5 µg/kg of body weight was derived from a NOAEL of 0.5 mg/kg of body weight per day by applying an uncertainty factor of 100 (for inter- and intraspecies variation). It was not considered necessary to include an additional uncertainty factor to allow for the tumour-promoting potential of lindane in view of the substantial database and numerous international evaluations of this
compound supporting the TDI.

Although exposure from food is decreasing, there may be substantial exposure from its use in public health and as a wood preservative. Therefore, only 1% of the TDI was allocated to drinking-water. The guideline value is thus 2 µg/litre (rounded figure).

References


15.21 MCPA

15.21.1 General description

Identity

CAS no.: 94-74-6
Molecular formula: C₉H₇ClO₃

MCPA is the common name for 4-chloro-2-methylphenoxyacetic acid.

Physicochemical properties (1-4)

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<th>Property</th>
<th>Value</th>
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<td>Water solubility</td>
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<tr>
<td>Organic carbon-water partition coefficient</td>
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<tr>
<td>Density</td>
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<tr>
<td>pKₐ</td>
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</tr>
</tbody>
</table>

Major uses

MCPA is a systemic hormone-type selective herbicide, readily absorbed by leaves and roots. Its uses include the control of annual and perennial weeds in cereals, grassland, and turf (1).

Environmental fate

MCPA did not volatilize from an aqueous solution (pH 7.0) heated for 13 days at 34-35 °C, nor was it hydrolysed at neutral pH (5). In aqueous solution at pH 8.3, MCPA had a photolytic half-life of 20-24 days in sunlight. In rice paddy water in the dark, it was totally degraded by aquatic microorganisms in 13 days (6). It undergoes various metabolic reactions.¹


MCPA can be expected to leach readily in most soils (7). Mobility increases as organic matter content decreases. Its half-life in soil was 15-50 days (5, 6). It degrades twice as quickly (6-12 days) when applied a second time to soil than after one application (15-28 days) (8).

15.21.2 Analytical methods

MCPA in water can be determined by a gas chromatographic method, after extraction with dichloromethane and esterification with diazomethane. The method sensitivity is about 0.1 µg/litre (9).
15.21.3 Environmental levels and human exposure

Water

In the USA, MCPA was found at levels of 0.04-0.54 µg/litre in four of 18 surface water samples analysed, but in none of 118 groundwater samples (4). It was detected in some groundwaters in Montana (maximum level 5.5 µg/litre) (4) and in two of 237 wells in Ontario (10).

Food

In surveys conducted during 1965-68 in the USA, MCPA was detected in food composites at a maximum concentration of less than 0.4 mg/kg. It was not detected in food composites of adult total diet samples during 1971-76 or in infant or toddler diet samples during 1974-75 (11).

15.21.4 Kinetics and metabolism in laboratory animals and humans

MCPA is readily absorbed from the gut of mice. After rats were exposed to MCPA, it was detected in all the organs tested (12). It is metabolized by the liver (13), 5-chloromethyl-catechol being one of its metabolites (14). Induction of microsomal oxidation by phenobarbital increases the rate of breakdown (13). Rats treated orally with MCPA excreted nearly all of it during the first 24 h after intake (90% in urine, 7% in faeces) (12). In rabbits and cattle, it is excreted rapidly, largely unchanged (15, 16). In humans, 50% of the total dose was detected in the urine within 48 h (17).

15.21.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Acute oral LD₅₀s for MCPA of 550 and 700 mg/kg of body weight have been reported in mice and rats, respectively (1).

Short-term exposure

After administration of MCPA (80.6% active ingredient) in the diet for 90 days to SPF weanling rats at doses of about 0, 2.5, 20, or 160 mg/kg of body weight per day, no compound-related effects were reported except for growth retardation and elevated relative kidney weights at the two highest doses. A NOAEL of 2.5 mg/kg of body weight per day was identified (18).

MCPA administered in the diet of CD rats for 3 months at doses of 0, 4, 8, or 16 mg/kg of body weight per day did not cause any adverse effects, except for increases in kidney weight in males at 16 mg/kg of body weight per day. A NOAEL of 8 mg/kg of body weight per day was identified from this study (19).

MCPA (94% a.i.) was administered orally to beagle dogs in two separate 13-week studies at dosing regimens of 0, 3, 12, or 48 mg/kg of body weight per day and 0, 0.3, 1, or 12 mg/kg of body weight per day. Decreased kidney and liver function, characterized by increases in blood urea, SGPT, and creatinine, were observed at doses as low as 3 mg/kg of body weight per day. Low prostatic weight and mucopurulent conjunctivitis were observed at higher doses. A NOAEL of 1 mg/kg of body weight per day was identified from these studies (20).

Beagle dogs were given oral doses of MCPA (95% a.i.) of 0, 0.15, 0.75, or 1.5 mg/kg of body weight per day for 1 year. Kidney toxicity was observed at the two highest doses. A NOAEL of 0.15 mg/kg of body weight per day was identified (21).
Long-term exposure

In a study in which Wistar rats (50 per sex per dose) were given MCPA (purity 84.8%) in their food at levels of 0, 20, 80, or 320 mg/kg for 2 years, a decrease in body weight gain, alterations of chemical and clinical parameters, and nephropathy were observed at the highest dose (22). In a study in which B6C21BRF1 mice (50 per sex per dose) were given MCPA orally at levels of 0, 20, 100, or 500 mg/kg for 2 years, a greater frequency of renal lesions as a result of chronic nephropathy was observed at the highest dose (23).

Reproductive toxicity, embryotoxicity, and teratogenicity

No effects on reproduction were found in rats exposed to MCPA (95% a.i.) at 0, 3.3, 10, or 30 mg/kg of body weight per day in the diet over two generations (24). After oral administration of MCPA (75% a.i.) at 0, 5, 25, or 100 mg/kg of body weight per day to mice on days 6 - 15 of gestation, significantly reduced fetal weights and delayed skeletal ossification were observed at the highest dose (25).

MCPA (purity not specified) was administered (0, 20, 50, or 125 mg/kg of body weight per day) by gavage to pregnant CD rats (16-38 per dose) on days 6 - 15 of gestation. No maternal or fetal toxicity or teratogenic effects were observed (26). The intragastric administration of technical MCPA (700 mg/kg) on days 9 or 10 of gestation to female Wistar rats caused an increase in the frequency of resorption, a reduction in fetal weight, and the appearance of major malformations (13).

After MCPA was administered (0, 5, 12, 30, or 75 mg/kg of body weight per day) by gavage to rabbits on days 6-18 of gestation, no fetotoxicity or teratogenicity was observed at any of the dose levels tested. Body weights of the does were markedly reduced in the group given 75 mg/kg of body weight per day. A fetal NOAEL of 75 mg/kg of body weight per day and a maternal NOAEL of 30 mg/kg of body weight per day were identified (27).

Mutagenicity and related end-points

MCPA is slightly mutagenic at the gene level in yeast and Drosophila (28, 29). It induces sister chromatid exchange in in vitro tests but has given contradictory results in vivo (30). It is inactive in gene mutation tests on bacteria and in in vivo cytogenetic tests (micronucleus and chromosomal aberrations) (31-34).

Carcinogenicity

MCPA (purity 84.8%) was administered to Wistar rats (50 per sex per dose) in their food at levels of 0, 20, 80, or 320 mg/kg for 2 years. No significant differences in the distribution of the various types of tumours in treated as compared with control animals were evident (22). Similarly, the oral administration of MCPA to B6C21BRF1 mice (50 per sex per dose) at levels of 0, 20, 100, or 500 mg/kg for 2 years did not cause any significant differences in the distribution of the various types of tumours as between the treated and control groups (23).

15.21.6 Effects on humans

Epidemiological investigations on MCPA have involved both the producers and users of chlorophenoxyacetic weedkillers, so that exposure to this product is generally accompanied by exposure to 2,4-D, 2,4,5-T, mocoprop, and dichlorprop. IARC carried out a comprehensive evaluation related to occupational exposures to chlorophenoxy herbicides, which were considered to show "limited evidence" of carcinogenicity (35).

15.21.7 Guideline value

There are only limited and inconclusive data on the genotoxicity of MCPA. IARC evaluated MCPA in 1983
and concluded that the available data on humans and experimental animals were inadequate for an evaluation of carcinogenicity (11). In further evaluations by IARC on chlorophenoxy herbicides in 1986 and 1987 it was concluded that evidence for their carcinogenicity was limited in humans and inadequate in animals (Group 2B) (35, 36). No adequate epidemiological data on exposure to MCPA alone are available. Recent carcinogenicity studies on rats and mice (22, 23) did not indicate that MCPA was carcinogenic.

A 1-year feeding study in dogs indicated a NOAEL of 0.15 mg/kg of body weight per day, based on the renal and liver toxicity observed at higher dose levels (21). Using this value and applying an uncertainty factor of 300 (100 for inter-and intraspecies variation and 3 for the inadequacy of the database), a TDI of 0.5 µg/kg of body weight can be calculated. An allocation of 10% of the TDI to drinking-water gives a guideline value of 2 µg/litre (rounded figure).

References


32. Buselmaier W, Rohrborn G, Propping P. (Mutagenicity investigations with pesticides in the host-
mediated assay and the dominant lethal test in mice.] Biologisches Zentralblatt, 1972, 91:311-325 (in German).


15.22 Methoxychlor

15.22.1. General description

Identity

CAS no.: 72-43-5
Molecular formula: C_{16}H_{15}Cl_{3}O_{2}

Methoxychlor is the common name for 1,1,1-trichloro-2,2-bis(4-methoxyphenyl)ethane. Other names include methoxy-DDT and DMDT. Technical methoxychlor contains about 88% of the p,p'-isomer together with more than 50 structurally related contaminants, including 1,1,1,2-tetrachloro-2-p-(4-methoxyphenyl)ethane, o,p'-dimethoxydiphenyltrichloroethane, o,o'-dimethoxydiphenyltrichloroethane, 1,1-bis(4-methoxyphenyl)-2,2-dichloroethene (DMDE), and o,p'-dimethoxydiphenyldichloroethene (1,2).

Physicochemical properties (1)

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<tr>
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<td>Physical state</td>
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<td>Melting point</td>
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<td>Boiling point</td>
<td>Decomposes</td>
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<td>Water solubility</td>
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<td>Log octanol-water partition coefficient</td>
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<tr>
<td>Density</td>
<td>1.41 g/cm³ at 25 °C</td>
</tr>
</tbody>
</table>

Organoeleptic properties

Methoxychlor has a light fruity smell (1). Its odour threshold in water is 4.7 mg/litre.¹

¹ Source: Hazardous Substances Data Bank, Bethesda, MD, National Library of Medicine.

Major uses

Methoxychlor is used as an insecticide to protect vegetables, fruit, trees, fodder cereals, farm animals, and pets against a variety of pests (3).
Environmental fate

Methoxychlor residues may persist in top soil for up to 14 months. Anaerobic biodegradation results mainly in dimethoxydiphenylchloroethane (DMDD) and the mono- and dihydroxy (demethylated) derivatives of methoxychlor and DMDD. Half-lives range from 1 week to 2 months. Aerobic degradation is much slower; half-lives are longer than 3 months. Methoxychlor may undergo indirect photolysis on the soil surface. The half-life for chemical hydrolysis in humid soils is about 1 year.1

1 Source: Hazardous Substances Data Bank, Bethesda, MD, National Library of Medicine.

In water, methoxychlor can be degraded to DMDE by ultraviolet light (4). The main route of disappearance from the water phase is volatilization; the half-life for volatilization from shallow waters is 4.5 days.1 Methoxychlor is adsorbed onto suspended solids or sediment. In sediments, the same biodegradation products form under anaerobic conditions as in soil. Methoxychlor may be ingested by some aquatic organisms and bioaccumulated, except in fish, which quickly metabolize it (4).

1 Source: Hazardous Substances Data Bank, Bethesda, MD, National Library of Medicine.

15.22.2. Analytical methods

Methoxychlor is determined by a liquid-liquid extraction/gas chromatographic procedure. The sensitivity is 0.001-0.01 µg of methoxychlor per litre for single-component pesticides and 0.05-1.0 µg of methoxychlor per litre for multiple-component pesticides for a 1-litre sample and electron-capture detection (5).

15.22.3. Environmental levels and human exposure

Air

Methoxychlor has been detected at a concentration of 254 ng/m³ in the ambient air near a pesticide plant in southern California (USA) [Source: Hazardous Substances Data Bank, Bethesda, MD, National Library of Medicine].

Water

Although methoxychlor is poorly soluble in water, it has been found in surface water, groundwater, and drinking-water. Only one out of 71 groundwater samples from rural areas contained methoxychlor at 0.09 µg/litre, but concentrations of up to 50 µg/litre were detected in both surface water and groundwater close to agricultural areas where it was applied (5). Drinking-water in two rural areas in the USA was reported to contain methoxychlor at concentrations of up to 312 µg/litre (mean 33 ng/litre) and 100 µg/litre (mean 23 ng/litre), respectively.1

1 Source: Hazardous Substances Data Bank, Bethesda, MD, National Library of Medicine.

Food

In studies performed in the USA from 1982 to 1985, the estimated daily intake of methoxychlor from food was 99 ng for men aged 25-30 years (1).

Estimated total exposure and relative contribution of drinking-water

The estimated total exposure will generally be less than 1 µg/person per day. Significant contributions may be made by drinking-water, but this is rare.

15.22.4. Kinetics and metabolism in laboratory animals and humans
Although methoxychlor is absorbed from the gastrointestinal tract, it does not accumulate in mammalian tissues (6). Body stores built up during periods of continuous exposure are cleared within a few weeks after cessation of exposure.† Excretion in faeces exceeds that in urine (7).

† Source: Hazardous Substances Data Bank, Bethesda, MD, National Library of Medicine.

In the presence of liver microsomes and NADPH, methoxychlor is oxidatively demethylated to form formaldehyde and phenolic metabolites (8-10). This reaction is not a precondition of the covalent binding of methoxychlor to the microsomal cytochrome P-450 (9). The phenolic metabolites competitively inhibit the binding of estradiol to its receptor; methoxychlor, like most of its technical impurities, is considered to be a proestrogen (1).

15.22.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Reported LD_{50}s for mammals are generally higher than 2 g/kg of body weight (1). The main effects of single high exposures are disturbances of glycogen metabolism (11) and fatty degeneration of organs (12).

Short-term exposure

A NOAEL of 140 mg/kg of body weight per day for testicular atrophy was reported in a 30-45-day study on rats (13). In a 56-day study, a LOAEL of 25 mg methoxychlor per kg of body weight per day increased pituitary prolactin levels in rats, an early effect of methoxychlor on the reproductive system (14).†

† Also based on data from Integrated Risk Information System (IRIS) data file, Cincinnati, OH, US Environmental Protection Agency.

Long-term exposure

Chronic toxicity tests on rats and mice exposed to technical grade methoxychlor during a 78-week period revealed NOAELs of 70 and 450 mg/kg of body weight per day, respectively (15). In rats fed methoxychlor at up to 80 mg/kg of body weight per day for 2 years, tumours occurred at a similar frequency as in controls. The main effect observed at higher doses was growth retardation (16). Pigs and dogs seemed to be less sensitive than rats and mice (17).

Reproductive toxicity, embryotoxicity, and teratogenicity

Methoxychlor reduced the weight of testicles, prostate, and seminal vesicles in rats (18) and disturbed spermatogenesis in sheep and rats (19,20). In a two-generation study with rats, maternal toxicity and various effects on reproductive functions were seen after repeated exposure of dams to 50 mg of methoxychlor per kg of body weight per day (LOAEL) (21). Fetal effects (deformed ribs) occurred only at higher doses (22).

Methoxychlor accelerates the displacement of developed embryos from the ovaries to the uterus (23). This can occur in rats at exposures as low as 25 mg/kg of body weight per day (LOAEL) (24).

A tentative maternal NOAEL of 5 mg of methoxychlor per kg of body weight per day was established in pregnant rabbits that lost their litters and exhibited reduced weight gain at or above 35 mg/kg of body weight (25). The high incidence of lung agenesis in all fetuses of all dose groups was unusual.†

† Source: Integrated Risk Information System (IRIS) data file, Cincinnati, OH, US Environmental
Protection Agency.

**Mutagenicity and related end-points**

Negative results were reported in various mutagenicity assays with or without metabolic activation.\(^1\) A weakly positive cell transformation response was obtained only with BALB/3T3-cells (1).

\(^1\) Source: Integrated Risk Information System (IRIS) data file, Cincinnati, OH, US Environmental Protection Agency.

**Carcinogenicity**

Although increases in adenomas in rats (AA Nelson, OG Fitzburgh, personal communication, 1951) and in total tumour numbers in rats (16,26) have been reported, they were considered to be insignificant.\(^1\) A significant increase in hepatocellular carcinomas in male and female rats together with a significant increase in ovarian carcinomas was reported (27), but there is some doubt regarding the statistical evaluation (1). Studies on Osborne-Mendel rats and B6C3F1 mice may indicate the potential carcinogenicity of methoxychlor (15) but are inadequate because of the lack of satisfactory histopathological investigations.

\(^1\) Source: Integrated Risk Information System (IRIS) data file, Cincinnati, OH, US Environmental Protection Agency.

Some positive evidence is provided by a 2-year study in which mice were given 750 mg of technical methoxychlor per kg of feed (27; KJ Davis, personal communication, 1969). Higher incidences of liver tumours occurred as compared with control animals. The males exhibited more testicle tumours and tumours of higher malignancy than the respective control animals.

Methoxychlor is likely to be a tumour promoter because it disturbs the metabolic cooperation between 6-thioguanidine-sensitive and -resistant V79-cells (28).

**15.22.6. Effects on humans**

A single dose of 2 mg/kg of body weight was without effect on liver, testicles, or small intestine (29). Doses of 0.5, 1.0, or 2.0 mg/kg of body weight per day administered orally to men and women over periods of 4-6 weeks (30) and 6-8 weeks (17) were without effect on body weight and several biochemical parameters. Tissue damage did not occur. The menstrual cycle and the volume of ejaculation were not affected, although a shortening of the neck of spermatozoa was observed in the first study (30).

**15.22.7. Guideline value**

In 1979, IARC assigned methoxychlor to Group 3 (31). Subsequent data suggest a carcinogenic potential of methoxychlor for liver and testis in mice, which may be due to the hormonal activity of proestrogenic metabolites of methoxychlor and may therefore have a threshold. The study, however, was inadequate because only one dose was used and because this dose may have been above the maximum tolerated dose (27). The genotoxic potential of methoxychlor appears to be negligible. It may be a tumour promoter.

The database for studies on long-term, short-term, and reproductive toxicity is inadequate. A teratology study in rabbits reported a systemic NOAEL of 5 mg/kg of body weight per day (25),\(^1\) which is lower than the NOAELs and LOAELs from other studies. This NOAEL was therefore selected for use in the derivation of a TDI. Using this NOAEL and applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for concern for threshold carcinogenicity and the limited database), a TDI of 5 µg/kg of body weight can be calculated. Allocation of 10% of the TDI to drinking-water results in a guideline value of 20 µg/litre (rounded figure).
Also based on data from Integrated Risk Information System (IRIS) data file, Cincinnati, OH, US Environmental Protection Agency.

References


\subsection{15.23 Metolachlor}
15.23.1. General description

Identity

CAS no.: 51218-45-2
Molecular formula: C\textsubscript{15}H\textsubscript{22}Cl\textsubscript{2}NO\textsubscript{2}

Metolachlor is the common name for 2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl) acet-o-toluidine.

Physicochemical properties (1)

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<td>Physical state</td>
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<td>Water solubility</td>
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<td>Octanol-water partition coefficient</td>
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Organooleptic properties

Metolachlor is odourless.

Major uses

Metolachlor is a selective herbicide for pre-emergence and preplant weed control in corn, soy beans, peanuts, sorghum, pod crops, potatoes, cotton, safflower and woody ornamentals (2).

Environmental fate

Metolachlor photodegrades slowly in aqueous solution exposed to sunlight (3). Its hydrolysis half-life is over 200 days at 20 °C (1). Volatilization from silty loam and sand has been observed (4). Metolachlor leaching is affected by adsorption onto soil organic matter, soil texture, precipitation, and water application. It can leach beyond the root zone in detectable amounts. The half-life in soil has been reported to range from 47 to 107 days (5). It can be metabolized by microorganisms (6).

15.23.2. Analytical methods

Metolachlor may be determined by gas chromatographic methods applicable to the determination of certain nitrogen/phosphorus-containing pesticides in water samples. The estimated detection limit ranges from 0.75 to 0.01 µg/litre (7).

15.23.3. Environmental levels and human exposure

Water

Metolachlor was found in 2091 of 4161 surface water samples and in 13 of 596 groundwater samples in the USA in 1988 (8). The 85th percentile of all non-zero samples was 12 µg/litre in surface water and 0.25µg/litre in groundwater. In another survey in the same country, metolachlor residues from agricultural use were detected in groundwater at levels ranging from 0.1 to 0.4 µg/litre. In a survey of 160 water bodies in Italy, metolachlor was found, if at all, at levels of less than 0.1µg/litre (9).

15.23.4. Kinetics and metabolism in laboratory animals and humans

Metolachlor is readily absorbed and excreted in the rat, male rats excreting 21.5% and 51.4% of the dose
administered in the urine and faeces, respectively, within 48 h. It is metabolized via dechlorination, O-methylation, N-dealkylation, and side-chain oxidation. Urinary and faecal metabolites include 2-ethyl-6-methylhydroxyacetanilide and N-(2-ethyl-6-methylphenyl)-N-(hydroxyacetyl)DL-alanine. No unchanged chemical was isolated (10).

15.23.5. Effects on laboratory animals and *in vitro* test systems

**Acute exposure**

Metolachlor has a low oral acute toxicity. Oral LD 50s in the rat are over 2000 mg/kg of body weight. The dermal LD 50 is over 10 000 mg/kg of body weight.1

1 Source: Registry of Toxic Effects of Chemical Substances (RTECS) file on line. Bethesda, MD, National Library of Medicine, National Institute for Occupational Safety and Health, 1977.

**Short-term exposure**

Beagle dogs given metolachlor at dose levels of 0, 50 (switched to 1000 mg/kg after 8 weeks), 150, or 500 mg/kg of diet for up to 15 weeks showed signs of toxicity only at the highest dose level (11).

In a 1-year study in beagle dogs, administration of metolachlor resulted in decreased kidney weight at the two highest dose levels. The NOAEL was determined to be 3.5 mg/kg of body weight per day (12).

**Long-term exposure**

In a 2-year study with albino mice fed diets containing metolachlor at levels of 0, 100, 300, or 1000 mg/kg, the only toxicological effects observed were decreased body weight gain and decreased survival in females at the highest dose level (13).

Albino Sprague-Dawley CD rats fed metolachlor for 2 years at dose levels of 0, 30, 300, or 3000 mg/kg showed decreased body weight gain and food consumption at the highest dose level (14).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Metolachlor was not teratogenic in gavage studies at daily dose levels up to and including 60 mg/kg of body weight in rats (15) and 360 mg/kg of body weight in rabbits (16). In a two-generation reproduction study, it decreased weight gain during lactation in pups at the highest dose level (equivalent to 14.7 mg/kg of body weight per day). The NOAEL in this study was 5 mg/kg of body weight per day (17).

**Mutagenicity and related end-points**

Metolachlor does not induce gene mutations in bacterial or mammalian cells and is negative in the dominant lethal assay and for unscheduled DNA synthesis *in vivo* and *in vitro* in rat hepatocytes and human fibroblasts (18).

**Carcinogenicity**

No evidence of carcinogenicity was found in a long-term dietary feeding study in albino mice at dose levels up to and including 3000 mg/kg (19). One study in rats showed an increase in the incidence of hepatocellular neoplasia in females receiving 3000 mg/kg in the diet for 2 years. One adenosarcoma and one fibrosarcoma were found in the nasal tissues of males at the highest dose only. No increase in tumour incidence was found in males or in females exposed to levels less than 3000 mg/kg. The increase in neoplasia in females was primarily due to an increased incidence of neoplastic nodules (14).
15.23.6. Effects on humans

Signs of intoxication by metolachlor include abdominal cramps, anaemia, ataxia, dark urine, methaemoglobinemia, cyanosis, hypothermia, collapse, convulsions, diarrhoea, jaundice, weakness, nausea, shock, sweating, vomiting, central nervous system depression, dizziness, dyspnoea, liver damage, nephritis, cardiovascular failure, dermatitis, sensitization, eye and mucous membrane irritation, corneal opacity, and reproductive effects.¹

¹ Source: HAZARDLINE. Bethesda, MD, National Library of Medicine, National Institutes of Health, 1985.

15.23.7. Guideline value

There is no evidence from available studies that metolachlor is carcinogenic in mice. In rats, an increase in liver tumours in females and a few nasal tumours in males have been observed. Metolachlor is not genotoxic.

Toxicity data are available from long-term studies in rodents and from a 1-year study in dogs. An apparent decrease in kidney weight was observed at the two highest dose levels in the 1-year dog study, giving a NOAEL of 3.5 mg/kg of body weight per day (12). An uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 because of some concern regarding carcinogenicity) was applied to this NOAEL to give a TDI of 3.5 µg/kg of body weight. A 10% allocation of the TDI to drinking-water results in a guideline value of 10µg/litre (rounded figure).

References


15.24 Molinate

15.24.1. General description

Identity

CAS no.: 2212-67-1
Molecular formula: C₉H₁₇NOS

Molinate is the common name for S-ethylazepane-1-carbothiate.

Physicochemical properties (1)

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<td>Octanol-water partition coefficient</td>
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Organoleptic properties

Molinate has an aromatic odour (1).
Major uses

Molinate is used to control germinating broad-leaved and grassy weeds. It is applied either before planting to water-seeded or shallow soil-seeded rice or post-flood, post-emergence in other types of rice culture (1).

Environmental fate

Volatilization is the main route of loss of molinate (active ingredient) from soil, taking place more easily on moist than on dry soils (2). Volatilization is also important in rice fields, increasing with temperature; the half-life is about 2 days at 28 °C. Photochemical degradation occurs to a lesser extent, and chemical hydrolysis and microbial degradation are negligible (3). Molinate is of low persistence in water and soil, with a half-life of about 5 days (4). In aerobic and flooded soils, half-lives were 8-25 and 40-160 days, respectively (1).

15.24.2. Analytical methods

Capillary gas chromatography with a selective nitrogen-phosphorus detector may be used for the determination of molinate, following extraction with methylene chloride. A detection limit of 0.03 µg/litre is possible (1).

15.24.3. Environmental levels and human exposure

Water

In 1987-88, water from 1288 drinking-water wells in the Lombardy region of Italy was analysed for molinate; it was detected in 27 wells at levels above 1 µg/litre and in 220 wells at levels between 0.1 and 1 µg/litre. In the Piedmont region, molinate was detected in 25 wells used as a source of drinking-water; in five of them, levels were above 1 µg/litre (5).

15.24.4. Kinetics and metabolism in laboratory animals and humans

Molinate is not absorbed percutaneously. In rats, it is metabolized primarily to the sulfoxide, then to mercapturic acid. Ring hydroxylation, mainly at the 3- and 4- positions, followed by glucuronidation and cleavage of the C-N bond to yield the imide, were also observed.¹ The active ingredient is quickly metabolized to carbon dioxide (18%) and eliminated through the urine (25%) and faeces (7-20%) within 3 days.²


15.24.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Acute oral LD₅₀s of 369 and 450 mg/kg of body weight have been reported for male and female rats, respectively (1).

Short-term exposure

Rats (15 per sex per dose) were given oral doses of technical active ingredient at 0, 35, 70, or 140 mg/kg of body weight per day in the diet for 90 days. Effects at 140 mg/kg of body weight per day included increased body weight, markedly decreased food intake, marked decrease in haemoglobin and haematocrit, increased relative weights of liver, kidney, adrenals, and thyroid, and histopathological
changes in liver, kidney, adrenals, testes, and ovaries. Similar but less marked changes occurred at 70 
mg/kg of body weight per day. There was also a slight increase in the lipoid content of the adrenals at 35 
mg/kg of body weight per day.3

3 US Environmental Protection Agency, Office of Pesticide Programs, reserved documentation.

In a study in which rats (15 per sex per dose) were fed technical active ingredient in their diets at 0, 8, 16, 
or 32 mg/kg of body weight per day for 90 days, effects observed at the highest dose included reduced 
food intake and weight gain, increased adrenal weight (females), and slight increases in relative weights 
for adrenals, thyroids, and testes in males and kidneys and adrenals in females. At the two highest doses, 
there were some cases of decreased differential leukocyte count (females), vacuolation of ovary stromal 
cells (females), and vacuolation of adrenocortical cells (both sexes). An increase in the content of lipid 
broides in the ovary and adrenal vacuolation was observed for all the treated groups.3

3 US Environmental Protection Agency, Office of Pesticide Programs, reserved documentation.

Dogs were given oral doses of technical active ingredient at 0, 15, 30, or 60 mg/kg of body weight for 90 
days. There were no clear signs of toxicity or modification of haematological and clinical parameters at the 
two lower doses, but a slight increase in thyroid weight was observed at the highest dose. No treatment-
related histopathological changes were observed.3

3 US Environmental Protection Agency, Office of Pesticide Programs, reserved documentation.

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Fischer rats (60 per sex per dose) were fed technical molinate in the diet for 104 weeks. Initial 
concentrations corresponded to daily intakes of 0, 8, 16, or 32 mg/kg of body weight, which were reduced 
after 18 weeks (following a failed attempt to produce the F1 generation) to 0, 0.6, 2.0, or 6.3 mg/kg of body 
weight per day. Rats were mated at 8-10 weeks from the beginning of the study. Administration of the diet 
was suspended 3 weeks before, and resumed 10-12 days after signs of mating were observed. Only one 
litter was born. At 21 weeks from the beginning of the study (3 weeks after reducing the diet 
concentration), all animals were mated again. Groups treated with 0, 0.6, 2.0, and 6.3 mg/kg of body 
weight per day generated 43, 18, 16, and 10 litters, respectively, of which 35, 8, 5, and 3 were alive at the 
age of 21 days; corresponding numbers of weanlings were 300, 37, 21, and 16, respectively (2).

Six groups of Sprague-Dawley rats were given technical molinate by gavage in corn oil at 0, 0.2, 4, 13, 30, 
or 60 mg/kg of body weight per day. There were no significant reductions in fertility parameters at 0.2 
mg/kg of body weight per day, but they were considerably reduced in both sexes at 4 mg/kg of body 
weight per day. Dose-related alterations in sperm morphology were also noted at this level. The necropsy 
data for pregnant females indicated a significant reduction in the number of viable fetuses per litter as a 
result of mating in the group given 4 mg/kg of body weight per day. An increase in the number of 
resorptions per litter as a result of matings with males in this group was also observed (2).

**Mutagenicity and related end-points**

Molinate did not show any significant mutagenic effect in the Ames test with five strains of *Salmonella 
typhimurium* with and without metabolic activation. It was also negative in assays for the induction of gene 
mutations in mouse lymphoma cells with and without metabolic activation, induction of micronuclei in CD-1 
mice *in vivo*, induction of sister chromatid exchange in Chinese hamster ovary cells with and without 
metabolic activation, and induction of unscheduled DNA synthesis in human HeLa cells with and without 
metabolic activation.1

1 US Environmental Protection Agency, Office of Pesticide Programs, reserved documentation.
**Carcinogenicity**

Fischer rats (60 per sex per dose) were fed technical molinate in the diet for 104 weeks at initial concentrations corresponding to daily intakes of 0, 8, 16, or 32 mg/kg of body weight, reduced after 18 weeks to 0, 0.6, 2.0, and 6.3 mg/kg of body weight per day. A greater than 90% incidence of interstitial-cell tumours of the testes was recorded in all groups (2).

Groups of 20 CAF₁ mice (BALBcJ × A/J) were given a molinate compound of unspecified composition for 99-101 weeks. Concentrations corresponded to intakes of 0, 3.6, 7.2, or 14.4 mg/kg of body weight per day. Adenomas, carcinomas, and lymphosarcomas of lungs, liver, kidney, spleen, and other organs were observed; there were no significant differences between the different dose groups (2). When BALB/cj females received doses of molinate up to 14 mg/kg of body weight per day, 10-12 days after mating with A/J males, and the F₁ mice (64-67 per dose) were fed the same diet for 76-78 weeks, tumour incidence was the same in all the groups (2).

15.24.6. Effects on humans

A review of epidemiological data based on the examination of workers involved in molinate production did not indicate any effect on fertility (4).

15.24.7. Guideline value

On the basis of the limited information available, molinate does not seem to be carcinogenic or mutagenic in animals. Evidence suggests that impairment of the reproductive performance of the male rat represents the most sensitive indicator of molinate exposure. However, epidemiological data based on the examination of workers involved in molinate production do not indicate any effect on human fertility.

The NOAEL for reproductive toxicity in the rat was 0.2 mg/kg of body weight per day (2), and this value was chosen as the basis for calculating a TDI for molinate. Using an uncertainty factor of 100 (for inter- and intraspecies variation), a TDI of 2 µg/kg of body weight was derived. An allocation of 10% of the TDI to drinking-water results in a guideline value of 6 µg/litre.

**References**


15.25 Pendimethalin
15.25.1. General description

Identity

CAS no.: 40487-42-1
Molecular formula: \( \text{C}_{13}\text{H}_{19}\text{N}_{3}\text{O}_{4} \)

Pendimethalin is the common name for \( \text{N}-(1\text{-ethylpropyl})-2,6\text{-dinitro-3,4-xylidine} \).

Physicochemical properties (1)

<table>
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<tr>
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<tr>
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<tr>
<td>Water solubility</td>
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</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Major uses

Pendimethalin is a selective herbicide, applied before emergence to cereals, maize, and rice, and with shallow soil incorporation before seeding bean, cotton, soy beans, and groundnuts. In vegetable crops, it is applied before emergence or transplanting, and it is also used to control suckers on tobacco (1).

Environmental fate

Pendimethalin is stable under both alkaline and acidic conditions (1). It is a moderately persistent herbicide that can give rise to long-lasting metabolites, mainly by photodegradation (2). Three by-products of soil fungal degradation have been identified as the result of ring hydroxylation, nitro group reduction, and complete \( \text{N} \)-dealkylation (3). Both pendimethalin and its metabolites bind tightly to soil particles, and the leaching potential is negligible (2). A half-life in soil of 30-90 days has been estimated (1). Pendimethalin has a low affinity for the water compartment. However, under anaerobic conditions, more polar metabolites of greater mobility are formed, and these can potentially contaminate both groundwater and surface waters (2).

15.25.2. Analytical methods

Pendimethalin can be determined by capillary gas chromatography with a selective nitrogen-phosphorus detector following extraction with methylene chloride. Confirmation by a second capillary column of different polarity is recommended.

15.25.3. Environmental levels and human exposure

Water

Pendimethalin was found at a concentration below 0.1 µ/litre in one of 76 drinking-water supplies examined in the Veneto Region in Italy in 1987-88 (4).

15.25.4. Kinetics and metabolism in laboratory animals and humans

Pendimethalin appears to be both poorly absorbed and rapidly excreted. About 95% is excreted within 24 h after oral administration, 75% being found in the faeces and 20% in the urine. Maximum tissue concentrations were found in the liver and kidney. Although most parent compound is excreted unchanged, the metabolites identified suggest that oxidation of the 4-methyl group on the phenyl moiety
and the N-alkyl side chain of the dinitro-substituted aniline are the predominant metabolic pathways (5).

15.25.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Pendimethalin is of low acute toxicity. LD_{50}s of 1050-1250 mg/kg of body weight in albino rats, 1340-1620 mg/kg of body weight in albino mice, and over 5000 mg/kg of body weight in beagle dogs have been reported (1).

Short-term exposure

In a study in which Charles River CD rats received pendimethalin in the diet at concentrations of 0, 100, 500, or 5000 mg/kg for 13 consecutive weeks, food intake and body weight gain were decreased only at 5000 mg/kg. A variety of indications of hepatotoxicity were also observed at this dose level. Absolute and relative kidney weights increased in males at 5000 mg/kg, and absolute and relative uterus and ovary weights decreased in females at 500 mg/kg (6).

Long-term exposure

CD-1 mice (75 per sex per dose) were given a diet containing the technical-grade compound at 0, 100, 500, or 2500 mg/kg for 18 months (dose doubled after 8 weeks) (7), and Long-Evans rats (60 per sex per dose) were fed a diet containing 0, 100, 500, or 2500 mg/kg for 2 years (highest dose doubled after 6 weeks) (8). At the highest doses, general toxic effects were observed both in the mouse (hyperglycaemia and increased thyroid and adrenal gland weights) and in the rat (increase in alkaline phosphatase levels, increased thyroid and kidney weights, hepatomegaly). Some toxic effects (hyperglycaemia in the mouse and hepatotoxicity in the rat) were present even at the lowest dose level of 100 mg/kg of diet (equivalent to 5 mg/kg of body weight per day). It was therefore not possible to establish a NOAEL.

Reproductive toxicity, embryotoxicity, and teratogenicity

Teratogenicity was not observed at the highest dose tested in rats (1000 mg/kg of body weight per day) (9,10) or rabbits (60 mg/kg of body weight per day) (11). In rats gavaged with pendimethalin on days 6-15 of gestation, embryotoxicity in the form of minor anomalies and reduced fetal weight was observed at 1000 mg/kg of body weight (9), and reduced ossification of the extremities was present at 250 and 500 mg/kg of body weight (10). Reproductive toxicity was not observed in a three-generation reproduction study in Long-Evans rats given pendimethalin in the diet at levels as high as 1000 mg/kg (12).

Mutagenicity and related end-points

Although genetic mutations were induced by pendimethalin with metabolic activation in Salmonella typhimurium, higher-purity technical material did not induce mutations in the same test system. Pendimethalin did not induce chromosomal aberrations, unscheduled DNA synthesis, or dominant lethal mutations (13-17).

Carcinogenicity

Neither CD-1 mice fed doses of pendimethalin up to 2500 mg/kg for 18 months (7) nor rats fed diets containing pendimethalin at up to 2500 mg/kg for 2 years showed evidence of carcinogenicity (8). However, these studies had important methodological limitations, including limited numbers of animals subjected to histological examinations.
15.25.6. Guideline value

Pendimethalin does not appear to have significant mutagenic activity. Long-term studies in mice and rats have not provided evidence of carcinogenicity; however, these studies have some important limitations.

The guideline value is based upon the LOAEL for liver toxicity (5 mg/kg of body weight per day) observed in the 2-year rat study (8). An uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a LOAEL instead of a NOAEL and for the limitations of the database) is used, giving a TDI of 5 µg/kg of body weight per day. An allocation of 10% of the TDI to drinking-water results in a guideline value of 20 µg/litre (rounded figure).

References


Cyanamid, 1985 (confidential information submitted to the Italian Ministry of Health).


### 15.26 Permethrin

#### 15.26.1. General description

**Identity**

CAS no: 52645-53-1  
Molecular formula: $\text{C}_{21}\text{H}_{20}\text{Cl}_{2}\text{O}_{3}$

Permethrin is the common name for 3-phenoxybenzyl (1RS)-$\text{cis}$, $\text{trans}$-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. It is a mixture of four stereoisomers of the (1R, $\text{trans}$), (1R, $\text{cis}$), (1S, $\text{trans}$), and (1S, $\text{cis}$) configurations. In most technical products, the $\text{cis}$:$\text{trans}$ ratio is about 2:3, and the 1R:1S ratio is 1:1 (racemic). The composition ratio of the above isomers is about 3:2:3:2 (1). Of the four isomers, the (1R, $\text{cis}$)- and the (1R, $\text{trans}$)-isomers are the two esters primarily responsible for insecticidal activity. The term permethrin is used here to refer to material with a $\text{cis}$:$\text{trans}$ ratio of 2:3, unless otherwise stated.

**Physicochemical properties (1)**

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<td>Boiling point</td>
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<td>Water solubility</td>
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</tr>
<tr>
<td>Log octanol-water partition coeff</td>
<td>6.5</td>
</tr>
</tbody>
</table>

**Organoleptic properties**

An organoleptic threshold in water of 0.2 mg/litre was reported in one study (2).

**Major uses**

Permethrin is a contact insecticide effective against a broad range of pests in agriculture, forestry, and public health. It is also used to control aquatic invertebrates, such as *Asellus aquaticus*, in water mains (3).

**Environmental fate**

Permethrin is photodegraded both in water and on soil surfaces. Ester cleavage and $\text{cis}$-$\text{trans}$ interconversion are the major reactions. At equilibrium, the $\text{trans}$-isomer constitutes 65-70% of the mixture. The major products of the ester cleavage of permethrin include 3-phenoxybenzaldehyde, 3-phenoxybenzoic acid, 3-phenoxybenzyl-3,3-dimethylacrylate, and benzyl alcohols, as well as the corresponding acids (1).

In soil, permethrin is rapidly degraded by hydrolysis and microbial action under aerobic conditions. Similar degradation processes seem to occur under anaerobic conditions but at slower rates. In laboratory...
studies, the soil half-life was approximately 28 days. The trans-isomer was more rapidly degraded than the cis-isomer, and ester cleavage was the major initial degradative reaction. In plants, permethrin degrades with a half-life of approximately 10 days (1,4).

15.26.2. Analytical methods

Permethrin may be determined by gas-liquid chromatography with an electron-capture or flame-ionization detector. The minimum detectable concentration is about 0.05 µg/litre (1).

15.26.3. Environmental levels and human exposure

Water

Surface waters may become contaminated by permethrin applied directly to water for mosquito control purposes, in discharges from production plants, and from agricultural sources. Concentrations as high as 0.8 mg/litre have been recorded in surface water. Levels in drinking-water have not been reported, but it is generally considered that permethrin is readily removed by conventional treatment methods and that neither cis- nor trans-permethrin reacts with chlorine under normal disinfection conditions (5). When permethrin is used to control aquatic invertebrates in water mains, concentrations of about 10 µg/litre will be present in the water for short periods (3).

Food

Exposure of the general population to permethrin is mainly via the diet. Residue levels in crops grown according to good agricultural practice are generally low. The resulting exposure is expected to be low, but precise data from total diet studies are lacking (1).

15.26.4. Kinetics and metabolism in laboratory animals and humans

Permethrin is readily absorbed when given orally. Distribution occurs rapidly in the body, mostly to adipose tissue, followed by liver, kidney, and brain.

Metabolism appears to be similar in all mammals, including humans (6,7). The main routes of metabolism for both the trans- and cis-isomers are ester cleavage and oxidation of the 4'-position of the terminal aromatic ring. Major metabolites formed include 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (Cl₂CA), in free and glucuronide form, and hydroxymethyl-Cl₂CA as a glucuronide conjugate (1).

Permethrin administered to mammals is almost completely eliminated from the body within several days. The trans-isomer is eliminated more quickly than the cis-isomer and is excreted mainly in the urine, whereas the cis-isomer is excreted in both the urine and faeces. Expiration as carbon dioxide plays a minor role in mammals. The very small amounts of unmetabolized permethrin found in fat and milk consist predominantly of the cis-isomer. Less than 0.7% of the administered dose was detected in the milk of goats or cows (1).

15.26.5. Effects on laboratory animals and in vitro systems

Acute exposure

Permethrin has a low acute oral toxicity in mammals, although the LD₅₀ varies considerably according to the administration vehicle used and the cis:trans isomeric ratio. The cis-isomer is the more toxic form. When corn oil is used as the vehicle, oral LD₅₀S are in the 0.5 g/kg of body weight range. Aqueous suspensions are the least toxic; LD₅₀S range from 3 to over 4 g/kg of body weight. The oral toxicities of the major metabolites of permethrin are lower than those of the parent compound. The major signs of acute intoxication are effects on the central nervous system, namely uncoordinated movements, whole-body
tremors, and loss of balance. Overt signs of toxicity do not appear until near-lethal doses (1,8).

**Short-term exposure**

No beagle dogs died when fed permethrin in gelatin capsules daily for 3 months at doses of up to 500 mg/kg of body weight per day. Growth, food consumption, clinical chemistry, haematology, and urological parameters were all normal, but doses of 50 mg/kg of body weight per day or higher resulted in significant increases in liver-to-body-weight ratios (9). No signs of toxicity were reported when beagle dogs received encapsulated doses of up to 250 mg/kg of body weight per day for 6 months (10).

**Long-term exposure**

In a 2-year study on Wistar rats fed permethrin at 0, 25, 40, or 125 mg/kg of body weight per day, tremors and hypersensitivity to noise were noted in rats at the highest dose. Significant increases in endoplasmic reticulum were detected only at this dose, although nonsignificant increases were noted at all levels in both sexes. The liver weights and liver-to-body-weight ratios were higher in all permethrin-treated males, but in females only in those that received 40 mg/kg of body weight per day. Kidney weights in males were increased at all dose levels (11).

In a 2-year study on Long-Evans rats fed permethrin in the diet at dose levels of 0, 20, 100, or 500 mg/kg (0, 1, 5, or 25 mg/kg of body weight per day), the estimated NOAEL was 5 mg/kg of body weight per day (12).

A lifetime (80% mortality) feeding study was carried out on Swiss-derived mice (70 per sex per dose) fed permethrin (cis 35-45%:trans 55-65%) at dose levels of 0, 250, 1000, or 2500 mg/kg of diet for 2 years. The mortality rate was normal, and growth was only slightly decreased at the two highest dose levels. There was a significant dose-dependent increase in liver-to-body-weight ratios in females at the two highest dose levels and in males at the highest dose level (11).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Dietary permethrin does not appear to adversely affect reproduction in rats or mice. Permethrin is not teratogenic to rats, mice, or rabbits at dose levels up to 225, 125, and 1800 mg/kg of body weight, respectively (1).

**Mutagenicity**

Both 2:3 and 1:3 permethrin have been tested in a number of in vitro and in vivo short-term assays for mutagenicity, all of which have given negative results (1).

**Carcinogenicity**

Studies carried out with both 2:3 and 1:3 permethrin have shown no evidence of carcinogenicity in rats (11,13). There is limited evidence of a weak carcinogenic potential in one strain of mice in which the incidence of pulmonary adenoma was increased in female mice at a dose of 250 mg/kg of body weight per day; however, it remained within historical control ranges for this strain (14). Moreover, the absence of positive mutagenic results suggests that this is probably an epigenetic mechanism. It has been concluded that the results of this study do not indicate that permethrin has any carcinogenic potential (15).

**15.26.6. Effects on humans**

Six forestry workers using permethrin exhibited symptoms such as itching and burning of the skin and itching and irritation of the eyes. Only one of them excreted urine containing detectable amounts (0.26 µg/ml) of permethrin metabolite (16).
Paraesthesia was induced in volunteers approximately 30 min after the application of permethrin solution (total 0.5 mg permethrin) to the earlobe (17); it peaked by 8 h and abated by 24 h. Of 10 volunteers treated with 15-40 ml of permethrin (1:3) (1%) head louse solution, which was allowed to dry and then washed out, three developed mild, patchy erythema, which faded 4-7 days later (1).

15.26.7. Guideline value

IARC has classified permethrin in Group 3, as there are no human data and only limited data from animal studies (18). Permethrin is not genotoxic.

Using a NOAEL of 100 mg/kg in the diet (equivalent to 5 mg/kg of body weight per day) obtained in a rat study (12) and an uncertainty factor of 100, JMPR recommended an ADI for 2:3 and 1:3 $\text{cis:trans}$-permethrin of 0.05 mg/kg of body weight (15).

Because there is significant exposure to permethrin from the environment, only 1% of the ADI is allocated to drinking-water. The guideline value is therefore 20 µg/litre (rounded figure). However, if permethrin is to be used for short periods as a larvicide for the control of mosquitos and other insects of health significance in drinking-water sources, the share of the ADI allocated to drinking-water may be increased.

References


11. Ishmael J, Lithfield MH. Chronic toxicity and carcinogenic evaluation of permethrin in rats and mice.


15.27 Propanil

15.27.1. General description

Identity

CAS no.: 709-98-8
Molecular formula: C₉H₉Cl₂NO

Propanil is the common name for 3',4'-dichloropropionanilide.

Physicochemical properties (1)

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<td>Water solubility</td>
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Major uses

Propanil is a contact post-emergence herbicide used mainly in rice to control broad-leaved and grass weeds. It is also used mixed with MCPA in wheat (1).
**Environmental fate**

Propanil is hydrolysed in acidic and alkaline media to 3,4-dichloroaniline and propionic acid. In water, propanil and 3,4-dichloroaniline are rapidly degraded by sunlight to phenolic compounds, which then polymerize (1). Propanil is biodegraded in soil to various metabolites, including 3,4-dichloroaniline, which rapidly binds to soil, propionic acid, which is further metabolized to carbon dioxide, 3,3',4,4'-tetrachloroazoxybenzene, and two isomeric forms of tetrachloroazobenzene (1)\(^1\) Propanil's half-life in soil is less than 5 days (1).


**15.27.2. Analytical methods**

Capillary gas chromatography with a selective nitrogen-phosphorus detector may be used for the determination of propanil, following extraction with methylene chloride. Confirmation by a second capillary column of different polarity is strongly recommended.

**15.27.3. Environmental levels and human exposure**

**Water**

Residues of less than 0.03 mg/litre were detected in 162 water samples collected from 16 rice fields treated with 0.4-2.8 kg of propanil per hectare, 1-120 days after application (2). It has only occasionally been detected in groundwater.

**15.27.4. Kinetics and metabolism in laboratory animals and humans**

Propanil and its metabolites do not appear to accumulate in tissues. It is hydrolysed by hepatic acylamidase, forming 3,4-dichloroaniline and propionic acid. Six metabolites have been detected in urine (3). When propanil was fed to a cow, 1.4% of the total dose was recovered in the faeces, but none was detected in urine or milk.\(^1\)


**15.27.5. Effects on laboratory animals and in vitro test systems**

**Acute exposure**

Propanil is of moderate acute toxicity; the oral LD\(_{50}\) is over 2500 mg/kg of body weight in the rat (1).

**Short-term exposure**

Groups of albino rats (10 per sex per dose) were given the technical product in doses of 100, 330, 1000, 3300, 10 000, or 50 000 mg/kg in the diet (equivalent to 5, 17, 50, 165, 500, or 2500 mg/kg of body weight per day) for 3 months. All the animals in the highest dose group died. There was an increase in polychromatophilia at dose levels of 330 mg/kg and higher as well as evidence of haemolytic anaemia at 3300 and 10 000 mg/kg. From this study, a NOAEL of 100 mg/kg (equivalent to 5 mg/kg of body weight per day) was identified (4).

**Long-term exposure**

Propanil was administered at concentrations of 0, 100, 400, or 1600 mg/kg in the diet to albino Wistar rats (25 per sex per dose) for 2 years. At 1600 mg/kg, rats exhibited increased mortality (males only), significant decreases in body weight, slightly lower haematocrit and haemoglobin values, and changes in
spleen-to-body-weight ratio (females only). The NOAEL in this study was 400 mg/kg, equivalent to 20 mg/kg of body weight per day (4).

In a 2-year study, beagle dogs were given propanil at concentrations of 0, 100, 600, or 3000 (raised to 4000 at the start of the 5th week) mg/kg in the diet. Significantly decreased body weight gains were evident at the highest dose level. No other effects attributable to propanil were observed (4).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Wistar rats administered technical-grade propanil in the diet (0, 100, 300, or 1000 mg/kg) for 11 weeks before mating and pregnancy did not exhibit any alterations in reproductive parameters (3).

**Mutagenicity and related end-points**

Propanil was inactive in *in vitro* tests on gene mutation, mitotic recombination, and repair and damage of DNA in prokaryotic and eukaryotic cells (4,5). It gave results that were essentially negative in the cytogenetic test on mice (induction of structural chromosomal aberrations) (4,6) and positive in radical apex barley cells (7). Its metabolite 3,3’,4,4’-tetrachloroazobenzene induces gene mutations in bacteria and fungal cells, as well as DNA repair synthesis in hepatic cultures in the rat (4,5,8).

**Carcinogenicity**

In a study in which groups of 50 Wistar rats were given oral propanil doses of 100, 400, or 1600 mg/kg for 24 months, histopathological tests did not reveal any carcinogenic effects. However, this study was limited and does not allow the evaluation of the carcinogenic potential of propanil (4).

**15.27.6. Effects on humans**

The probable oral lethal dose is 0.5-5 g/kg of body weight. Exposure produces local irritation and central nervous system depression. Ingestion causes local irritation with a burning sensation in the mouth, oesophagus, and stomach, gagging, coughing, nausea, and vomiting followed by headache, dizziness, drowsiness, and confusion.¹


Workers from a pesticide plant who were exposed to the propanil metabolite 3,4-dichloroaniline showed signs of methaemoglobinemia. Of the 28 workers exposed to 3,4-dichloroaniline and propanil, 17 showed signs of chloracne, which is attributed to the presence of the contaminants 3,3’,4,4’-tetrachloroazobenzene or 3,3’4,4’-tetrachloroazoxybenzene (9).

**15.27.7. Guideline value**

Propanil is not considered to be genotoxic. However, at least one of its environmental metabolites (tetrachloroazobenzene) is genotoxic. Data from a limited study in rats do not provide evidence of carcinogenicity.

Long-term exposure to propanil results in red blood cell toxicity. A TDI of 5 µg/kg of body weight was established, based on the NOAEL of 5 mg/kg of body weight per day from the 3-month rat feeding study (4) and applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the short duration of the study and the limitations of the database).

Based on an allocation of 10% of the TDI to drinking-water, the guideline value is 20 µg/litre (rounded figure). In applying this guideline, authorities should consider the possible presence in water of more toxic environmental metabolites.
References


15.28 Pyridate

15.28.1. General description

**Identity**

CAS no.: 55512-33-9  
Molecular formula: $C_{19}H_{23}O_{2}N_{2}SCl$

Pyridate is the common name for $O$-(6-chloro-3-phenyl-4-pyridazinyl) S-octyl carbonothioate.

**Physicochemical properties (1)**

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<td>Water solubility</td>
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</table>

**Major uses**

Pyridate is a foliar-acting contact herbicide used for the control of annual dicotyledonous plants and some grassy weeds. It controls weeds selectively in cereals, maize, rice, and other crops (1).
Environmental fate

Pyridate has low water solubility and relatively low mobility. It is not persistent and is rapidly hydrolysed, photodegraded, and biodegraded. Its primary environmental metabolite (6-chloro-4-hydroxy-3-phenylpyridazine) is also not persistent but is more mobile. Under favourable conditions, the environmental half-life is of the order of a few days (2). Pyridate is rapidly metabolized and inactivated in plants that have a high tolerance for the active ingredient (3).

15.28.2. Analytical methods

The main pyridate metabolite, 6-chloro-4-hydroxy-3-phenylpyridazine, may be determined by high-performance liquid chromatography followed by ultraviolet absorption at 254 or 280 nm (4).

15.28.3. Environmental levels and human exposure

Water

This compound has rarely been found in water supplies (2).

15.28.4. Kinetics and metabolism in laboratory animals and humans

After oral administration to rats, pyridate is rapidly absorbed by the gut and distributed to the organs. It is quickly excreted, mainly in the urine (5,6). Three radioactive metabolites have been identified in the urine of rats, the most important being the hydrolysis product 6-chloro-4-hydroxy-3-phenylpyridazine (7). Pyridate is hydrolysed in the blood and in artificially prepared intestinal juices of rats (8,9).

15.28.5. Effects on laboratory animals and in vitro test systems

Acute exposure

The acute LD50 for rats was reported to be 2000 mg/kg of body weight (1).

Short-term exposure

The technical product (purity 90.3%) was administered in the diet to pure-bred beagle dogs for 1 year at doses of 0, 60, 240, or 2000 mg/kg, corresponding to about 0, 2, 8, and 77 mg/kg of body weight per day, without causing death. Dose-related vomiting and diarrhoea were observed in all groups; erythemas and alopecia were observed in some animals. At the highest dose, decreased adrenal weight, increased thyroid weight, decreased alpha-globulin, albumin, and lactate dehydrogenase, and increased platelet number were observed. From this study, a NOAEL of 8 mg/kg of body weight per day has been identified (10).

Long-term exposure

The technical product (90.3% purity) was administered to Wistar SPF rats for 2 years in the diet at doses of 0, 80, 400, or 2500 mg/kg, corresponding to about 0, 3.5, 18, or 114 mg/kg of body weight per day. At the highest dose, the product caused reduced body growth, reduced food consumption, decreased transaminases of lacticdehydrogenasis and alkaline phosphatase, as well as increased kidney weight. At the middle dose, increased kidney weight was observed. From this study, a NOAEL of 3.5 mg/kg of body weight per day has been derived (11).

In a 2-year study, the product was administered to Swiss mice in the diet at doses of 0, 200, 1000, or 5000 mg/kg, corresponding to about 0, 24, 120, and 600 mg/kg of body weight per day. Mortality ranged from 24% to 52% and was lower in animals receiving the highest dose. The product caused decreased body
growth in both sexes at the highest dose, as well as an increased relative weight of the liver in males at
the middle and high doses. From this study, a NOAEL of 24 mg/kg of body weight per day was identified
(12).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a three-generation study, Wistar rats were fed technical pyridate in their diets at doses of 0, 80, 400, or
2500 mg/kg. No changes in the reproductive cycle were observed (13). In two studies conducted on rats
and rabbits, pyridate was found not to possess teratogenic potential (14,15).

Mutagenicity and related end-points

Pyridate does not induce gene mutations in bacteria, somatic mutation in mice, DNA repair synthesis in rat
hepatocyte cultures, loss of X and Y chromosomes in Drosophila, micronuclei in mice, or transformation in
vitro (16-21).

Carcinogenicity

In a study in which the technical product (90.3% purity) was administered to Wistar SPF rats in the diet for
2 years at doses of 0, 80, 400, or 2500 mg/kg (0, 3.5, 18, or 114 mg/kg of body weight per day), non-dose-
related excesses of benign and malignant phaeochromocytomas in males, mammary fibroadenomas in
females, and thyroid adenomas in both sexes were observed (11). No excesses of tumours of any type
were observed when the product was administered to Swiss mice at doses of 0, 200, 1000, or 5000 mg/kg
in the diet (0, 24, 120, or 600 mg/kg of body weight per day) (12).

15.28.6. Guideline value

IARC has not evaluated pyridate. It has been tested in long-term feeding studies in rats and mice; no
evidence of carcinogenicity was noted in either species. The available evidence indicates that it is not
mutagenic.

A NOAEL of 3.5 mg/kg of body weight per day was established based on increased kidney weight in a 2-
year study on rats (11). A TDI of 35 µg/kg of body weight was calculated by applying an uncertainty factor
of 100 (for inter- and intraspecies variation) to this NOAEL. An allocation of 10% of the TDI to drinking-
water gives a guideline value of 100 µg/litre (rounded figure).

References


2. Drinking water quality: guidelines for selected herbicides. Copenhagen, WHO Regional Office for
Europe, 1987 (Environmental Health 27).


4. Method of analysis for determination of 6-chloro-4-hydroxy-3-phenylpyridazine in leaching water. Linz,

5. Österreichische Studiengesellschaft für Atomenergie, Institute of Biology, Seibersdorf Research Centre.
Orientating kinetic trials with 14C-pyridate. Linz, Chemie Linz, 1978 (unpublished study submitted to
WHO).

6. Österreichische Studiengesellschaft für Atomenergie, Institute of Biology, Seibersdorf Research Centre.
Distribution of 14C-pyridate after single oral application in rats. Linz, Chemie Linz, 1979 (unpublished study


15.29 Simazine
15.29.1. General description

*Identity*

CAS no.: 122-34-9  
Molecular formula: C₇H₁₂ClN₃

Simazine is the common name for 6-chloro-\(N,N'-\)diethyl-1,3,5-triazine-2,4-diylamine.

*Physicochemical properties (1-3)*

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>225-227 °C (decomposes)</td>
</tr>
<tr>
<td>Density</td>
<td>1.302 g/cm³ at 20 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>5 mg/litre at 20 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>8.1 (\times) 10⁻⁴ Pa at 20 °C</td>
</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Major uses*

Simazine is a pre-emergence herbicide used to control broad-leaved and grass weeds in artichokes, asparagus, berries, broad beans, citrus fruits, coffee, cocoa, hops, maize, oil palms, olives, orchards, ornamentals, sugar-cane, tea, tree nurseries, turf, and vineyards, as well as in non-crop areas (1).

*Environmental fate*

Under normal climatic conditions, volatilization and photodegradation are not expected to be important processes in the dissipation of simazine from soil (2) [Source: Hazardous Substances Data Bank. Bethesda, MD, National Library of Medicine]. Its half-life in soil has been reported as 46-174 days (3). Simazine can be degraded through hydrolysis and \(N\)-dealkylation (4,5). It is mineralized slowly.¹ Even though it has a low solubility in water, it has been classified as a leacher (6).


15.29.2. Analytical methods

Simazine can be determined by a capillary column gas chromatographic method applicable to the determination of certain nitrogen/phosphorus-containing pesticides in water. In this method, the sample is extracted with methylene chloride, the extract is concentrated, and the compounds are separated by capillary-column gas chromatography, after which they are measured by means of a nitrogen-phosphorus detector. The estimated detection limit is 75 ng/litre (7).

15.29.3. Environmental levels and human exposure

*Water*

Typical levels of 1-2 µg/litre have been reported in groundwater in the USA (8). Contamination of groundwater by simazine has also been reported in Italy and Germany (9,10).

15.29.4. Kinetics and metabolism in laboratory animals and humans

Simazine is absorbed by the gut of rats and mice and distributed to various tissues; the highest concentrations are found in the spleen, liver, and kidney (11). In 24-h urine samples from female rats given simazine orally, conjugated mercapturates of hydroxysimazine, 2-hydroxy-4-amino-6-ethylamino-s-
triazine, and 2-hydroxy-4,6-diamino-s-triazine were found, accounting for 6.8%, 6.1%, and 14% of the administered dose, respectively (12). In 24-h urine samples from male rats that had received simazine by gavage, the di-N-dealkylated metabolites were present at higher levels than the mono-N-dealkylated ones (13). Following oral administration in rats, most simazine was excreted within 7 days, mainly in the urine (11).

15.29.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Oral LD50s for simazine have been reported to be greater than 5000 mg/kg of body weight in the rat, mouse, and rabbit (1,2).

Long-term exposure

Dogs (2 per sex per dose) were treated orally for 105 weeks with 0, 15, 150, or 1500 mg of simazine per kg of feed. No deaths or evident toxic effects were caused by the treatment, apart from a transitory increase in aspartate aminotransferase in two out of four animals at the highest dose. The NOAEL was 150 mg/kg, corresponding to 5 mg/kg of body weight per day (14).

Dogs (4 per sex per dose) were treated for 2 years with doses of 0, 20, 100, or 1250 mg/kg in the diet. At the highest dose, the treatment caused cachexia in one animal of each sex, as well as reduced weight gain in one female, accompanied by a transitory reduction in food consumption. There was also a reduction in erythrocyte parameters in both males and females and an increase in thrombocytes in males. At 100 mg/kg, there were both reduced weight gain and reduced erythrocyte parameters in females. From this study, a NOAEL of 20 mg/kg, corresponding to 0.8 mg/kg of body weight per day, can be derived (15).

Technical simazine (purity not specified) was administered orally for 2 years at doses of 0, 10, 100, or 1000 mg/kg of feed to Sprague-Dawley rats (70 per sex per dose; satellite groups were used in order to study chronic toxicity). The NOAEL for this study was 10 mg/kg (0.52 mg/kg of body weight per day), based on weight changes and haematological parameters (16).

Reproductive toxicity, embryotoxicity, and teratogenicity

No reproductive effects were observed in a three-generation study in which technical simazine was administered to rats at doses up to 100 mg/kg of feed (17). In studies on rats and rabbits, the compound was not embryotoxic or teratogenic when administered at doses that were not maternally toxic (18,21).

Mutagenicity and related end-points

Simazine did not induce micronuclei in mice. It induced a small increase in the frequency of sister chromatid exchange in human cells in vitro but not in Chinese hamster cells. It also induced chromosomal aberrations in plants and dominant lethal mutations in Drosophila, but not aneuploidy in yeast or gene conversion or mitotic recombination in bacteria (22).

Carcinogenicity

Technical simazine (purity not specified) was administered orally for 2 years at doses of 0, 10, 100, or 1000 mg/kg of feed to Sprague-Dawley rats (70 per sex per dose). At the end of the experiment, the numbers surviving were, in order of increasing dose, 27, 24, 31, and 42 in males and 24, 23, 17, and 14 in females. Mortality was frequently related to tumours of the hypophysis, which were observed more often in the females; there were no significant differences between the various treated groups and the controls. In the females treated at 100 and 1000 mg/kg, there was an increase in mammary tumours with, in order of increasing dose: adenomas and fibroadenomas: 24/70, 31/70, 70/70, 45/70; and carcinomas: 14/70,
In the group receiving 1000 mg/kg, an increase in cystic glandular hyperplasia was observed. In the males, there was an increase in adenomas and carcinomas of the liver: 1/70, 3/70, 4/70, 6/70; a decrease in pancreatic tumours: 4/70, 14/70, 1/70, 0/70; and a decrease in benign phaeochromocytomas: 12/70, 14/70, 10/70, 3/70. The NOAEL from this study was 10 mg/kg (0.52 mg/kg of body weight per day) (16).

The same technical simazine was administered orally for 95 weeks at doses of 0, 40, 1000, or 4000 mg/kg to groups of Swiss CD-1 mice (60 per sex per dose) (23). At the end of the experiment, the numbers surviving were, in order of decreasing dose, 19, 15, 13, and 15 in males and 26, 26, 35, and 25 in females. There were no significant differences between the treated groups and the controls for the various types of tumours observed.

15.29.6. Effects on humans

A total of 124 cases of contact dermatitis were noted in the former USSR among workers manufacturing simazine and propazine. Serious cases lasting 7-10 days involved erythema, oedema and a vesiculopapular reaction that sometimes progressed to the formation of bullae (24). One study showed an association between ovarian tumours and exposure to triazine herbicides (25), but the number of subjects was small. IARC evaluated the carcinogenicity of simazine in humans and concluded that adequate data were not available (22).

15.29.7. Guideline value

Simazine does not appear to be genotoxic in mammalian systems. Recent studies have shown an increase in mammary tumours in the female rat but no effects in the mouse. IARC has classified simazine in Group 3 (22).

Based on a study in the rat, a NOAEL of 0.52 mg/kg of body weight per day has been established for carcinogenicity and long-term toxicity (16). By applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for possible carcinogenicity), a TDI of 0.52 µg/kg of body weight was derived. An allocation of 10% of the TDI to drinking-water gives a guideline value of 2 µg/litre (rounded figure).

References


15.30 Trifluralin

15.30.1. General description

Identity

CAS no.: 1582-09-8
Molecular formula: C_{13}H_{16}F_{3}N_{3}O_{4}

Trifluralin is the common name for a,a,a-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine.

Physicochemical properties (1)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>48.5-49 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>&lt;1 mg/litre at 27 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>1.37 × 10^{-2} Pa at 25 °C</td>
</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>4.69</td>
</tr>
</tbody>
</table>

Major uses

Trifluralin is a pre-emergence herbicide used for the control of annual grasses and broad-leaved weeds in beans, brassicas, cotton, groundnuts, forage legumes, orchards, ornamentals, transplanted peppers, soy beans, sugar-beet, sunflowers, tomatoes, and vineyards (1).

Environmental fate

Trifluralin has low water solubility. It is dissipated by photodecomposition, volatilization, and biodegradation (2-4). Trifluralin has a high affinity for soil and is relatively immobile (5); the half-life is 3-18 weeks, depending on soil type and geographical location (2). Its degradation in soil involves a series of oxidative dealkylation steps, the reduction of the nitro group, and oxidative cyclization (6), resulting in the formation of small quantities of several transformation products as well as significant amounts of nonextractable soil-bound compounds that reside in the fulvic and humic acid fractions of soils (7).

15.30.2. Analytical methods

Trifluralin may be extracted with dichloromethane and determined by capillary gas chromatography with a nitrogen-phosphorus detector. The method sensitivity is 0.05 µg/litre (8).

15.30.3. Environmental levels and human exposure

Water

In the USA, trifluralin was found in 172 of 2047 surface water samples and in one of 507 groundwater samples analysed. The 85th percentile of the levels in all non-zero surface water samples was 0.54 µg/litre (9). It was not found in 229 drinking-water supplies (mainly groundwater) analysed in Italy (10).

15.30.4. Kinetics and metabolism in laboratory animals and humans

Oral doses of trifluralin were not readily absorbed by the gastrointestinal tract of the rat. About 80% of the dose was found in the faeces, the remaining appearing in the urine. Even though unchanged trifluralin was isolated from the faeces (<8% of the administered dose), the absorbed fraction was extensively metabolized. N-dealkylation and nitro reduction were two of the principal metabolic pathways. The metabolic fate of trifluralin was similar in the rat and in the dog (11). Following intraperitoneal
administration to rats, it was detected at higher concentrations in the fat than in the liver (12).

15.30.5. Effects on laboratory animals and in vitro test systems

Acute exposure

Oral LD$_{50}$s of over 10 g/kg of body weight for rats, 0.5 g/kg of body weight for mice, and over 2 g/kg of body weight for rabbits and dogs have been reported (1).

Short-term exposure

Beagle dogs were fed trifluralin at doses of 30, 150, or 750 mg/kg in the diet for 12 months. Effects at the highest doses included slightly decreased mean body weight gain, slight changes in plasma lipids, and a statistically significant increase in liver weight. A NOAEL of 30 mg/kg, equivalent to an average daily intake of 0.75 mg/kg of body weight, was derived, based on mild hepatic effects (13).

Long-term exposure

The effects of trifluralin were studied in Fischer rats at doses of 813, 3250, or 6500 mg/kg in the diet for 24 months (14); in Wistar rats at doses of 200, 800, or 3200 mg/kg in the diet for 24 and 28 months (15); in NMRI mice at doses of 50, 200, or 800 mg/kg in the diet for 104 weeks (16); and in beagle dogs at doses of 400 or 1000 mg/kg in the diet for 3 years (17). These tests were not adequate by today’s standards because of methodological limitations and contamination problems.

Reproductive toxicity, embryotoxicity, and teratogenicity

Trifluralin is embryotoxic in the rat (18,19) and in the rabbit (21,22) at dose levels that are clearly maternally toxic; however, it is not teratogenic in these species.

Mutagenicity and related end-points

Studies on the mutagenicity of trifluralin show that low-purity technical trifluralin may contain nitroso contaminants and is mutagenic. High-purity trifluralin, in contrast, is not (20).

Carcinogenicity

Trifluralin containing the impurity nitrosodipropylamine was assayed for carcinogenicity in oral experiments on the rat and mouse (15,16,23,24). For each species, the first experiment was carried out with trifluralin that contained large amounts of the impurity. Carcinogenic effects on the liver, lungs, and stomach in female mice were observed, as well as equivocal indications of carcinogenicity in the rat thyroid. In the second experiment in each species, the trifluralin used contained the impurity at 0.4 mg/kg, two orders of magnitude less than in the previous studies. No carcinogenic effects were found in mice. In rats, however, there was an excess, limited to males treated with high doses, of granular cellular meningiomas (a rare benign tumour whose normal occurrence in rats is unknown). The incidence of thyroid tumours was not statistically significant and was not dose-related.

On the basis of a recent evaluation, IARC concluded that there is limited evidence in experimental animals for the carcinogenicity of technical-grade trifluralin (20).

15.30.6. Effects on humans

In a study in the USA, the use of trifluralin was associated with an increased risk for non-Hodgkin lymphoma. In contrast, a study of ovarian cancer in Italy did not suggest an association with trifluralin exposure. In both studies, the numbers of exposed subjects were small. A larger study in the USA showed
no association with leukaemia (20). IARC concluded that there is inadequate evidence in humans for the carcinogenicity of trifluralin (20).

15.30.7. Guideline value

IARC recently evaluated technical-grade trifluralin and assigned it to Group 3 (27). No evidence of carcinogenicity was found in a number of long-term toxicity/carcinogenicity studies with pure (>99%) test material. Trifluralin of high purity does not possess mutagenic properties. Technical trifluralin of low purity may contain nitroso contaminants and has been found to be mutagenic.

A NOAEL of 0.75 mg/kg of body weight per day was selected based on a 1-year feeding study in dogs (13). This species is the most sensitive for the mild hepatic effects on which the NOAEL was based. Using this NOAEL and an uncertainty factor of 100 (for inter- and intraspecies variation), a TDI of 7.5 µg/kg of body weight was derived. A guideline value of 20 µg/litre (rounded figure) is recommended, based on an allocation of 10% of the TDI to drinking-water.

Authorities should note that some impure technical grades of trifluralin could contain potent carcinogenic compounds and therefore should not be used.

References


13. 12 Months oral toxicity (feeding) study in Beagle dogs. Indianapolis, IN, Eli Lilly, 1984 (unpublished study submitted to WHO).

14. The chronic toxicity of compound trifluralin given as a component of the diet to Fischer 344 rats for two years. Indianapolis, IN, Eli Lilly, 1980 (unpublished study submitted to WHO).


18. Multiple generation study in the rat. Indianapolis, IN, Eli Lilly, 1984 (unpublished study submitted to WHO).

19. Testing for embryotoxicity in Wistar rats following oral administration. Indianapolis, IN, Eli Lilly, no date (unpublished study submitted to WHO).


21. Embryotoxicity study in the rabbit (oral administration). Indianapolis, IN, Eli Lilly, 1984 (unpublished study submitted to WHO).


15.31 Chlorophenoxy herbicides (excluding 2,4-D and MCPA)

15.31.1. General description

Identity

Although many chlorophenoxy compounds are used in weed control, only dichlorprop, 2,4-DB, 2,4,5-T, fenoprop, mecoprop, and MCPB will be considered here.

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS no.</th>
<th>Molecular formula</th>
<th>Other names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichlorprop</td>
<td>120-36-5</td>
<td>C₉H₈Cl₂O₃</td>
<td>2,4-dichlorophenoxypropionic acid; 2,4-DP</td>
</tr>
<tr>
<td>2,4-DB</td>
<td>94-82-6</td>
<td>C₁₀H₁₀Cl₂O₃</td>
<td>4-(2,4-dichlorophenoxy) butyric acid</td>
</tr>
<tr>
<td>2,4,5-T</td>
<td>93-76-5</td>
<td>C₈H₈Cl₅O₃</td>
<td>2,4,5-trichlorophenoxyacetic acid</td>
</tr>
</tbody>
</table>
Physicochemical properties (1)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting point (°C)</th>
<th>Water solubility (mg/litre)</th>
<th>Vapour pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichlorprop</td>
<td>168-175</td>
<td>350 at 20 °C</td>
<td>Negligible</td>
</tr>
<tr>
<td>2,4-DB</td>
<td>117-119</td>
<td>46 at 25 °C</td>
<td>Negligible</td>
</tr>
<tr>
<td>2,4,5-T</td>
<td>153</td>
<td>150 at 25 °C</td>
<td>$1 \times 10^{-5}$ Pa at 25 °C</td>
</tr>
<tr>
<td>Fenoprop</td>
<td>179-181.6</td>
<td>140 at 25 °C</td>
<td>Practically nonvolatile</td>
</tr>
<tr>
<td>Mecoprop</td>
<td>94-95</td>
<td>620 at 20 °C</td>
<td>$&lt;1 \times 10^{-5}$ Pa at 20 °C</td>
</tr>
<tr>
<td>MCPB</td>
<td>100</td>
<td>44 at 20 °C</td>
<td>$&lt;1 \times 10^{-5}$ Pa at 20 °C</td>
</tr>
</tbody>
</table>

Major uses

Chlorophenoxy herbicides are used extensively throughout the world for the control of broad-leaved annual and perennial weeds in a variety of agricultural crops. They are also used in brush control in non-agricultural areas, to control broad-leaved aquatic weeds, and as a pre-harvest treatment to reduce early drop in apple orchards. Chlorophenoxy herbicides are usually applied post-emergence, often in combination with other herbicides.

Chlorophenoxy compounds are derived from chlorophenols, which may be contaminated by dioxins; the herbicide preparations, especially those containing the trichlorophenoxy acids, may therefore also be contaminated by dioxins.

Environmental fate

Residues of chlorophenoxy herbicides in the environment are the consequence of the direct application of these compounds to agricultural and non-agricultural areas. Biodegradation is the primary route of elimination from the environment; photolysis and hydrolysis also contribute to their removal.

The half-life for the degradation of dichlorprop to 2,4-dichlorophenol in soil is estimated to be 8-12 days (2-4); disappearance is essentially complete in 14 days (5). The degradation half-life of 2,4,5-T in soil is 12-59 days (2,4); residues do not usually persist beyond one growing season (3). Reported half-lives of fenoprop are in the range 8-17 days (2,3,6) to 3-4 months (7). The primary degradation product of 2,4,5-T and fenoprop is 2,4,5-trichlorophenol (1,8). Mecoprop is broken down in soil to 4-chloro-4-methylphenol (1), with a half-life of 7-9 days (9); residues of mecoprop have been reported to persist in soil for up to 2 months following application (10). The half-life of MCPB in soil is 4-6 days (3,9), unless the soil microorganisms have been acclimatized to the herbicide, in which case its half-life is less than 1 day (3). MCPB degrades in soil to MCPA (9) and 4-chloro-2-methylphenol (1). The half-life of 2,4-DB in soil is less than 7 days (1).

The chlorophenoxy herbicides are considered to have only marginal potential for leaching to groundwater (11). In basic waters, phenoxy herbicide esters are hydrolysed to the anionic forms; in acidic waters, photodegradation or vaporization predominates, depending on the ester. The photolytic half-life of 2,4,5-T in near-surface waters has been calculated to be 15 days (12). Fenoprop was essentially cleared from three Louisiana ponds within 5 weeks of treatment (13).

15.31.2. Analytical methods
Common methods for the determination of chlorophenoxy herbicides in water include solvent extraction, separation by gas chromatography, gas-liquid chromatography, thin-layer chromatography, or high-performance liquid chromatography, with electron capture or ultraviolet detection. Detection limits range from 1 µg/litre to 1 mg/litre (8,14). Specific ion monitoring mass spectroscopy can be used for confirmation (8). Chemical derivatization of chlorophenoxy acids and salts is often necessary, as they are practically nonvolatile and too polar to chromatograph directly (15).

15.31.3. Environmental levels and human exposure

Air

Chlorophenoxy herbicides may be transported in the atmosphere in the form of droplets, vapour, or powder following application by spraying. Concentrations of particulate 2,4,5-T of up to approximately 0.045 µg/m³ in air have been found in Pullman, Washington, whereas up to 0.04 mg of 2,4,5-T per kg was present in a dust sample collected in Cincinnati, OH (16).

Water

Mecoprop was not detected in a survey of 91 farm wells in Ontario (Canada) during 1984 (detection limit 0.1 µg/litre) (17). 2,4,5-T was not detected in 602 samples of private and municipal drinking-water supplies in 90 communities in three Canadian provinces surveyed from 1978 to 1986 (detection limits 0.005-0.05 µg/litre) (18). Fenoprop was detected in only a small number of drinking-water supplies in several national and regional surveys in the USA (detection limits not specified) (7).

In 1984, 2,4,5-T was detected in groundwater near a dump in New Brunswick (Canada) at a concentration of 3.7 µg/litre (18). In other studies, 2,4,5-T concentrations as high as 17 µg/litre have been reported in groundwater (19). Groundwater in the Netherlands was found to contain a maximum concentration of 2 µg of mecoprop per litre (20). Most groundwaters surveyed in the USA contained less than 0.1 µg of fenoprop per litre (7).

In a survey of three Canadian agricultural river basins, dichlorprop, mecoprop, 2,4-DB, and MCPB were found in 4%, 3%, 0.5%, and 0%, respectively, of 447 surface water samples at mean concentrations of 0.1-3.1 µg/litre (detection limits 0.1-0.5 µg/litre) (21). Concentrations of 2,4,5-T in 1548 samples of Canadian surface waters surveyed from 1980 to 1985 ranged from not detectable to 0.04 µg/litre (detection limit 0.01 µg/litre); concentrations of fenoprop in 1339 surface water samples from western Canada were less than 4 ng/litre (22). Surface water in the Netherlands has been found to contain maximum mecoprop and MCPB concentrations of 1-10 µg/litre; a maximum concentration of 0.1 µg of mecoprop/litre was found in infiltrated river bank water (20).

Food

Chlorophenoxy herbicides may be present in food as a result of their direct application to crops; however, concentrations are normally low (16). In a Canadian total diet study conducted from 1976 to 1978, MCPB, 2,4,5-T, and fenoprop were not detected (detection limits 300, 100, and 50 µg/kg, respectively) (23). Neither 2,4,5-T nor 2,4-DB was detected in a survey of 14 492 domestic and imported foods in the USA in 1987 (24). Dichlorprop was present at levels of up to 0.1 mg/kg in cereal grains at harvest time (25).

Estimated total exposure and relative contribution of drinking-water

Based on maximum residue limits for 2,4,5-T established by the Codex Alimentarius Commission (26), the theoretical maximum daily intake of 2,4,5-T from food ranges from 10.8 to 68.8 µg/day, with a global mean of 24.6 µg/day for a 60-kg adult. The average daily intake of 2,4,5-T in food is estimated to be 0.2 ng/kg of body weight per day for a male or female aged 25B30, based on the concentrations found in foods in the
15.31.4. Kinetics and metabolism in laboratory animals and humans

In general, chlorophenoxy herbicides are rapidly absorbed from the gastrointestinal tract and evenly distributed throughout the body; accumulation in human tissues is not expected. A steady-state level in the human body will be achieved within 3-5 days of exposure. The herbicides are eliminated mainly in the urine, mostly unchanged, although fenoprop may be conjugated to a significant extent. Biological half-lives of chlorophenoxy herbicides in mammals range from 10 to 33 h; between 75% and 95% of the ingested amount is excreted within 96 h. Dogs appear to retain chlorophenoxy acids longer than other species as a result of relatively poor urinary clearance and thus may be more susceptible to their toxic effects. Metabolic conversions occur only at high doses. The salt and ester forms are rapidly hydrolysed and follow the same pharmacokinetic pathways as the free acids.

15.31.5. Effects on laboratory animals and in vitro test systems

**Dichlorprop**

*Acute exposure*

The oral LD₅₀s of dichlorprop in rats and mice are 800 and 309 mg/kg of body weight, respectively.

*Short-term exposure*

Slight liver hypertrophy was seen in rats receiving a dietary dose of 50 mg dichlorprop per kg of body weight per day for 3 months; no adverse effects were noted in rats consuming 12.4 mg/kg of body weight per day.

*Long-term exposure*

In a 2-year study in Fischer 344 rats (80 per sex per dose), animals were fed diets containing 0, 100, 300, 1000, or 3000 mg of dichlorprop per kg. At 3000 mg/kg, survival was slightly reduced in females; body weight was depressed by 10% in both males and females; there was diffuse hepatocellular swelling and deposition of brown pigment in liver cells; and rats exhibited mild anaemia, as indicated by decreased haematocrit, erythrocyte count, and haemoglobin. The incidence of brown pigment in the kidneys was increased in both sexes in the 1000 and 3000 mg/kg groups, possibly indicative of slight degeneration of the tubular epithelium. Urinary specific gravity and protein were decreased in males exposed to 300 mg/kg and in females exposed to 1000 mg/kg. The authors considered the NOAEL for renal toxicity to be 100 mg/kg (3.64 mg/kg of body weight per day) in males and 300 mg/kg (13.1 mg/kg of body weight per day) in females.

*Reproductive toxicity, embryotoxicity, and teratogenicity*

No adverse effects on reproduction or fertility were reported in a three-generation reproduction study in which groups of rats were fed diets containing 125, 500, or 2000 mg of dichlorprop per kg. In a study in which doses of 0, 100, 200, 300, 400, or 500 mg of dichlorprop per kg of body weight were orally administered to pregnant mice on days 6-15 of pregnancy, embryotoxic effects were observed at 300 mg/kg of body weight, and skeletal malformations occurred at 400 mg/kg of body weight. No toxic effects were reported in a summary of a study in which pregnant rats were given doses of 0, 5, 30, 100, or 200 mg of dichlorprop per kg of body weight by gavage on days 4, 10, 13, and 18, although it was shown to cross the placental barrier.
Mutagenicity and related end-points

Dichlorprop was not mutagenic in eight strains of Salmonella typhimurium in the absence of mammalian metabolic activation (35). However, it induced respiration-defective mutant cells of Saccharomyces cerevisiae (36) and caused mitotic gene conversion and gene mutation in S. cerevisiae (37,38) and DNA damage in Escherichia coli (39) at concentrations of 4.0 mg/ml or greater. Dichlorprop did not significantly influence testicular DNA synthesis in male mice following a single intraperitoneal dose of 200 mg/kg of body weight (40).

Carcinogenicity

In an 18-month oncogenicity study, Charles River CD-1 mice were fed diets containing 0, 25, 100, or 300 mg of dichlorprop per kg. The incidence of benign hepatomas was increased in males in the highest dose group, but the authors speculated that this was due to an increased metabolic burden on the liver, which impaired the metabolic process necessary for the suppression of neoplastic development; they concluded that dichlorprop was not carcinogenic at the doses administered (41).

2,4-DB

Acute exposure

The oral LD$_{50}$ of 2,4-DB in rats is 700 mg/kg of body weight (30).

Short-term exposure

Beagle dogs (4 per sex per dose) were fed diets containing 0, 316, 1000, or 3160 mg of 2,4-DB per kg for 2 weeks, then given the compound in capsules daily for 7 weeks at doses equivalent to 0, 8, 25, or 80 mg/kg of body weight per day. An additional group of 4 males and 4 females were given capsules containing the equivalent of 2.5 mg/kg of body weight per day for 13 weeks. At 25 and 80 mg/kg of body weight per day, effects on animals included diarrhoea, inactivity, depression, weakness, cysts, increased mortality, reduced body weight and food consumption, haematological effects, abnormal blood chemistry and urinalysis, jaundice, increased relative thyroid, liver, spleen, and kidney weights, and decreased relative testes weight. At 8 mg/kg of body weight per day, serum alanine aminotransferase was elevated and nodular lymphoid hyperplasia of the gastric mucosa occurred in one of four males and one of four females (both with gross lesions). The NOAEL was considered to be 2.5 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1973).

In a study in which groups of Charles River rats were fed diets containing 0, 100, 316, 1000, or 3160 mg of 2,4-DB per kg for 3 months, relative liver and kidney weights were significantly elevated in males in the 3160 mg/kg group and in females in the 1000 and 3160 mg/kg groups; a significant decrease in the relative adrenal weight in females at 3160 mg/kg was also noted. All animals consuming 1000 mg of 2,4-DB per kg and above had hepatocytic hypertrophy, as did one male and one female exposed to 316 mg/kg. The NOAEL for hepatocytic hypertrophy was considered to be 100 mg/kg, equivalent to 5 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1973).

Long-term exposure

Groups of Charles River Crl:CD (SD)BR rats were fed diets containing 0, 60, 600, or 1800 mg of 2,4-DB per kg (equivalent to doses of 0, 3, 30, or 90 mg/kg of body weight per day) for 2 years. Rats in the highest dose group exhibited adverse effects such as decreased body weight gain, lower spleen and liver weights, higher relative kidney weights, and altered blood chemistry and haematological parameters. Rats consuming 30 mg of 2,4-DB per kg of body weight per day had decreased mean body weight gain, lower mean body weights (females only), altered blood chemistry and haematological parameters (although to a lesser extent than in the highest dose group), and slightly but not significantly lower mean heart weight
Reproductive toxicity, embryotoxicity, and teratogenicity

In a two-generation reproduction study in which rats were fed diets containing 0, 60, 300, or 1500 mg of 2,4-DB per kg (equivalent to doses of 0, 3, 15, or 75 mg/kg of body weight per day), effects noted in the highest dose group included reduced ovarian weight, lower mean birth weights, slightly longer gestation periods, fewer total pups per litter at birth, greater numbers of dead pups at birth, and extremely high mortality during the lactation period. No effects on reproduction were reported in the 300 mg/kg group, although offspring had increased mean liver, spleen, and kidney weights and decreased mean thymus, heart, lung, and adrenal weights (43).

In a teratological study in New Zealand white rabbits, groups of pregnant does were given doses of 2.5, 12, or 60 mg of 2,4-DB per kg of body weight per day in capsules on days 5-15 or 5-20 of gestation. In the highest dose group, many rabbits lost weight, three rabbits aborted their litters before day 29, and three others resorbed their litters. No adverse effects were noted in the does in the low or intermediate dose groups. The mean body weight of live fetuses was significantly reduced in the group receiving 12 mg/kg of body weight per day. The researchers concluded that 2,4-DB was not teratogenic in rabbits but had an indirect embryotoxic effect at 12 mg/kg of body weight per day (May and Baker, Ltd., unpublished data, 1974).

In a study in which groups of pregnant Charles River mice were fed diets containing 0, 400, or 2000 mg of 2,4-DB per kg on days 6-15 of gestation, the number of resorption sites per dam was increased in the mice consuming 2000 mg/kg, as were the mean number of dead fetuses per female and the number of females with dead fetuses; the mean number of live fetuses per female was reduced in this group. The NOAEL for fetotoxic effects in this study has been considered to be 400 mg/kg (Department of National Health and Welfare, Canada, unpublished data, 1973), equivalent to 60 mg/kg of body weight per day (44).

Mutagenicity and related end-points

2,4-DB did not induce point mutations in Salmonella typhimurium (35) but was weakly mutagenic in the CHO/HGPRT forward mutation assay (45). It caused a significant increase in chromosomal aberrations in Chinese hamster ovary cells, but only in the absence of metabolic activation (46). No unscheduled DNA synthesis was induced in rat hepatocytes (47).

Carcinogenicity

Tumour incidence was not increased in a 2-year study in which groups of rats were fed 0, 3, 30, or 90 mg of 2,4-DB per kg of body weight per day in the diet (42). Except in the highest dose group, in which survival was significantly reduced, a possible dose-response relationship in the incidence of hepatocellular carcinomas was reported in male mice fed 0, 25, 250, or 750 mg of 2,4-DB per kg of diet (equivalent to doses of 0, 3.75, 37.5, and 112.5 mg/kg of body weight per day) for 78 weeks. Tumour incidence was not increased in females (48).

2,4,5-T

Acute exposure

The oral LD50s for 2,4,5-T range from 100 mg/kg of body weight in the dog to 300 mg/kg of body weight in the rat and 425 mg/kg of body weight in the hamster (30).
Long-term exposure

Sprague-Dawley rats (50 per sex per dose in treated groups, 86 per sex in the control group) were fed 2,4,5-T (practically free from dioxin contamination) at doses equivalent to 0, 3, 10, or 30 mg/kg of body weight per day in the diet for 2 years. Rats of both sexes in the highest dose group had reduced body weight gain, elevated urinary excretion of porphyrins, and hepatocellular swelling and paleness. Animals in the groups receiving 10 and 30 mg/kg of body weight per day had increased relative kidney and liver weights. Dose-related increases in mineralization in the renal pelvis were noted in the kidneys of female rats fed diets containing 10 and 30 mg/kg of body weight per day. The NOAEL for reduced body weight gain, increased liver and kidney weights, and renal toxicity was considered to be 3 mg/kg of body weight per day (49).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a three-generation reproduction study, Sprague-Dawley rats were fed dietary doses of dioxin-free (<0.03 µg/kg) 2,4,5-T equivalent to 0, 3, 10, or 30 mg/kg of body weight per day. Reductions were seen in neonatal survival in the F2 generation and decreases in fertility in the F30 litter in the group consuming 10 mg/kg of body weight per day; postnatal survival, relative liver weights, and thymus weights were reduced in several litters in the highest dose group. The NOAEL for reproductive effects was 3 mg/kg of body weight per day (50).

Results of various reproductive studies indicate that 2,4,5-T not appreciably contaminated with dioxin caused teratogenic effects (cleft palate and kidney malformations) only in mice at doses above 20 mg/kg of body weight (51,52). Some skeletal anomalies (delayed ossification) were observed in rats exposed to fetotoxic doses in excess of 50 or 100 mg/kg of body weight (53,54). There was no teratogenic response in other studies in rats, rabbits, or monkeys (55).

Mutagenicity and related end-points

The results of several short-term genotoxicity tests on 2,4,5-T have been reviewed by IARC (55,56). Negative results were obtained for several species of bacteria and yeast, but mutagenicity was observed in the yeast Saccharomyces cerevisiae. 2,4,5-T was not mutagenic in several in vivo tests in mammalian cells, including a mouse micronucleus test and dominant lethal tests in mice and rats. Chromosomal aberrations were induced in in vitro tests in bone marrow cells of gerbils but not in spermatogonia of Chinese hamsters. Aneuploidy was not induced in Drosophila or in oocytes of rats treated in vivo.

Carcinogenicity

No compound-related increase in the incidence of tumours was reported in a study in which Sprague-Dawley rats were fed doses equivalent to 0, 3, 10, or 30 mg of 2,4,5-T per kg of body weight per day in the diet for 2 years (51). 2,4,5-T was not carcinogenic when administered orally or subcutaneously in mice (55,57). Although a significant increase in the incidence of total tumours was reported in female C3Hf mice given approximately 12 mg/kg of body weight per day for life (58), the small number of animals employed in the tests and the high incidence of spontaneous tumours in the controls suggest that the evidence for carcinogenicity in animals is inadequate (56).

Fenoprop

Acute exposure

The oral LD50 of fenoprop in rats is 650 mg/kg of body weight (30).
**Short-term exposure**

In a 90-day study in which rats were fed concentrations of 100, 300, 1000, 3000, or 10 000 mg of the sodium salt of fenoprop per kg in the diet, body weight gain was depressed at 300 mg/kg and above and liver weight was increased at 100 mg/kg; animals in all treatment groups, except females in the lowest dose group, had liver and kidney damage (59). In a study in which beagle dogs were fed doses equivalent to 53, 160, or 530 mg of fenoprop per kg of body weight for 89 days, no adverse effects were reported except for a decrease in body weight gain in females in the highest dose group (59).

**Long-term exposure**

In an 18-month study, rats were fed diets containing a potassium salt of fenoprop at concentrations equivalent to doses of 0, 0.26, 0.8, 2.6, or 7.9 mg/kg of body weight per day. Males in the highest dose group had reduced body weight and increased relative kidney weight. The NOAEL was considered to be 2.6 mg/kg of body weight per day (29). In a similar study in which male and female rats were fed the potassium salt of fenoprop in the diet at concentrations equivalent to 5.3, 16, 53, or 160 mg of fenoprop per kg of diet for 2 years, increased kidney weight was observed in males in the 160 mg/kg group. The authors concluded that the NOAEL was 53 mg/kg, equal to 3.18 mg/kg of body weight per day (59).

In a study in which beagle dogs were fed concentrations of 30, 101, or 300 mg of fenoprop per kg of diet as the potassium salt for 2 years, severe liver pathology was reported in both sexes in the highest dose group after 1 year and in males consuming 101 mg of fenoprop per kg of diet after 2 years. The NOAELs were considered to be 30 mg/kg in male dogs and 101 mg/kg in females, equivalent to 0.75 and 2.5 mg/kg of body weight per day, respectively (59).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

A decrease in fetal body weight and an increase in maternal weight (probably due to increased liver weight) were observed when pregnant CD-1 mice were given 400 mg of fenoprop per kg of body weight per day by gavage or subcutaneously on days 12-15 of gestation; toxic effects appeared to be dependent on the vehicle and route of administration (60).

No teratogenic effects were reported in a study in which pregnant rats were given 100, 150, 200, or 300 mg of fenoprop per kg of body weight per day by gavage on days 6-15 of gestation, based on gross examination of the fetuses (Dow Chemical Company, unpublished data, 1970; cited in reference 16). Fenoprop increased the incidence of cleft palate by 7% and 3%, respectively, for oral and subcutaneous administration (60). It was reported to be nonteratogenic in both the CD rat and the CD-1 mouse (dose not specified) (61). Significant effects on fetal mortality and birth weight were observed in litters of pregnant Sprague-Dawley rats given fenoprop (containing <0.05 mg of dioxin per kg) at doses of 25-100 mg/kg of body weight per day on days 6-15 of gestation (62). It caused teratogenic effects on the fetuses (dose levels not specified), including skeletal anomalies such as cleft palate, retarded ossification and extra cervical ribs, microphthalmia, and cardiovascular abnormalities. Similar effects were observed in animals treated with the propylene glycol butyl ether ester of fenoprop (62).
Mutagenicity and related end-points

Fenoprop was not mutagenic in the Salmonella typhimurium assay (35).

Carcinogenicity

No increase in the incidence of tumours was reported in a 2-year study in which beagle dogs were fed doses of fenoprop ranging from 0.9 to 9.9 mg/kg of body weight per day in the diet (29). No significant increase in the incidence of tumours was noted in mice administered 46.4 mg of fenoprop per kg of body weight per day initially by gavage (28 days) and subsequently in the diet for 76-77 weeks (57).

Mecoprop

Acute exposure

The oral LD50s for rats and mice are 650 and 369 mg/kg of body weight, respectively (30).

Short-term exposure

Weanling SPF-Wistar rats were fed diets containing 0, 50, 400, or 3200 mg of mecoprop per kg for 90 days; effects experienced at the highest dose included significantly decreased blood haemoglobin content and erythrocyte counts, a decrease in neutrophils (females only), a significant increase in alkaline phosphatase activity, and decreased relative kidney weights. Effects at 400 mg/kg included decreased relative kidney weights and significantly decreased numbers of erythrocytes. The NOAEL for effects on the kidney and blood parameters was considered to be 50 mg/kg, equivalent to 3 mg/kg of body weight per day (63).

Beagle dogs were fed diets containing mecoprop at concentrations equivalent to doses of 0, 4, 16, or 64 mg/kg of body weight per day for 13 weeks; effects experienced at the highest dose included depressed body weight gain, increased relative weights of heart, liver, kidney, brain, and lungs, increased blood urea levels, decreased blood haemoglobin levels (weeks 6 and 13), decreased packed cell volume and red blood cells (week 13), and decreased lymphocyte and increased neutrophil counts (week 6). Effects at 16 mg/kg of body weight per day included depressed body weight gain and a decrease in packed cell volume and red blood cell values (week 6). The NOAEL for blood parameters and body weight gain is considered to be 4 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1980).

In a study in which rats were fed diets containing 0, 100, 400, 1000, or 2500 mg of the diethanolamine salt of mecoprop per kg of feed for 7 months, animals consuming 400 mg/kg and above showed reduced erythrocyte counts, haemoglobin, and packed cell volume. Relative liver weight was increased in females in the 400 mg/kg group and in males in the 2500 mg/kg group. Relative kidney weights were increased in rats in all treatment groups. The NOAEL for effects on blood parameters and organ weights was 100 mg/kg of diet for the diethanolamine salt, equal to a dose of 67 mg of mecoprop per kg of diet, and equivalent to 4 mg/kg of body weight per day (64).

Long-term exposure

Male Wistar rats fed mecoprop over a period of 52 weeks at doses of 20, 100, or 400 mg/kg in the diet experienced an increase in relative kidney weights at the two highest doses. When the rats were fed the same doses for 24 months, there was a statistically significant increase in the absolute kidney weights of the males dosed at 100 and 400 mg/kg and in the relative kidney weights of those dosed at 400 mg/kg. No treatment-related effects were reported in female rats. The NOAEL of 20 mg/kg is equivalent to 1 mg/kg of body weight per day (65).
Reproductive toxicity, embryotoxicity, and teratogenicity

Groups of pregnant rats were given doses of 20, 50, or 125 mg of mecoprop per kg of body weight per day on days 6-15 of gestation. Increased intrauterine deaths, decreased crown-rump lengths, and an increased incidence of delayed or absent ossification of the sternebrae were reported in the highest dose group, although no toxic effects were noted in the dams (66). There were no teratogenic or fetotoxic effects in offspring of groups of 15 pregnant rabbits receiving doses of 12, 30, or 75 mg of mecoprop per kg of body weight per day on days 6-18 of gestation (66). In a study in which mice were given doses of 0, 100, 200, 300, 400, 500, or 700 mg of mecoprop per kg of body weight per day by the oral route on days 6-15 of pregnancy, doses of 300 mg/kg of body weight per day and above were embryotoxic, and skeletal malformations were observed at doses of 400 mg/kg of body weight per day and above (33). In a summary of a study in which pregnant rats and mice were given the potassium salt of mecoprop (0-330 mg/kg of body weight per day for rats and 0-150 mg/kg of body weight per day for mice) by gavage on days 4, 10, 13, and 18, a significant increase in the number of fetuses with hydroureter was induced by the highest dose. Mecoprop was found to readily cross the placental barrier (34).

Mutagenicity and related end-points

Mecoprop was not mutagenic in reverse-mutation assays with Salmonella typhimurium (35,67) and Escherichia coli (67). It was not mutagenic in Streptomyces coelicolor in the forward-mutation test (68), nor did it induce point mutation, nondisjunction, or mitotic crossing-over in Aspergillus nidulans (69,70). It did induce mitotic gene conversion in yeast cultures heteroallelic at two loci (71).

Carcinogenicity

No significant increase in the incidence of tumours was reported in Wistar rats fed mecoprop in the diet at concentrations of 0, 20, 100, or 400 mg/kg for 2 years (65).

MCPB

Acute exposure

The oral LD₅₀s of MCPB in rats and mice are 680 and 800 mg/kg of body weight, respectively (30).

Short-term exposure

In a 13-week study, rats were fed diets containing 0, 4, 12, or 40 mg of MCPB per kg of body weight per day. No effects on mortality, food intake, body weight gain, haematology, clinical chemistry, urinalysis, organ weights, gross pathology, or histopathology were reported. The NOAEL was considered to be 40 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1988). It should be noted, however, that the doses administered did not approach the maximum tolerated dose; thus, the potential short-term effects of MCPB were not fully assessed.

In a study in which beagle dogs were fed dietary concentrations of MCPB of 0, 160, 480, or 1600 mg/kg of diet for 13 weeks, no compound-related effects were reported on mortality, appearance, behaviour, food intake, body weight, haematology, clinical chemistry, urinalysis, or gross pathology. Weights of testes were depressed in males in the highest dose group; spermatogenesis was absent; the seminiferous tubules, which appeared atrophic, and the epididymis contained spermatozoal precursors and/or giant cells; and the prostate was not fully developed and appeared atrophic. The NOAEL for testicular effects is 480 mg/kg of diet, equivalent to 12 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1988).
**Mutagenicity and related end-points**

MCPB was not mutagenic in bacterial reverse-mutation assay systems in five strains of *Salmonella typhimurium* and one strain of *Escherichia coli* (35,67). MCPB administered subcutaneously at doses of 200 mg/kg enhanced the mutation frequency of *S. typhimurium* in NMRI mice (72). It did not produce any deviation from normality when tested for chromosome loss, nondisjunction, or induced X-Y recombination in male *Drosophila* (73).

**15.31.6. Effects on humans**

**Acute exposure**

Dichlorprop is rated as moderately to highly acutely toxic to humans (74). 2,4,5-T is considered to be moderately acutely toxic; the symptoms produced by high oral doses include nausea, vomiting, drowsiness, fever, increases in pulse and respiration, shock, coma, and death (75). No adverse effects were reported following the ingestion of a single dose of 1 mg of fenoprop per kg of body weight by eight human volunteers (76). The symptoms described in case histories of acute poisoning by weedkiller solutions containing mecoprop include coma, fever, respiratory problems, myotonia, muscle cramps, skeletal muscle damage, electrocardiographic changes, decreased blood pressure, distended abdomen, and rhabdomyolysis with renal failure (77-79).

**Carcinogenicity**

Until recently, most epidemiological studies of the effects of chlorophenoxy herbicides dealt with populations exposed in the 1950s and 1960s, when the trichlorophenol-based herbicides 2,4,5-T and fenoprop were contaminated with polychlorinated dioxins and furans, including 2,3,7,8-tetrachlorodibenzodioxin (TCDD); the effects observed may therefore have been a consequence of the presence of the dioxin contaminants. In addition, most epidemiological studies on chlorophenoxy herbicides conducted to date have involved multiple exposures to chemical agents, including other pesticides and synthetic organic compounds.

In a series of case-referent studies conducted in Sweden in the late 1970s and early 1980s, strong associations were noted between soft tissue sarcomas (STS) and multiple lymphomas (including Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL)) and the use of chlorophenoxy herbicides by agricultural or forestry workers (80-82). Although the methodology employed has been extensively criticized, these studies served to focus attention on STS, NHL, and HD as the outcomes of interest in succeeding case-referent and cohort studies.

The association between STS and chlorophenoxy herbicide use observed in the Swedish studies has not been confirmed in other case-referent studies (83-87). Although a number of cohort studies of occupationally exposed workers have been conducted, the small size of many of them limits their usefulness in assessing the relationship between STS and the herbicides.

The risk for malignant lymphoma (HD + NHL) was almost five times greater for agricultural and forestry workers exposed to a mixture of chlorophenoxy herbicides than for controls in the case-referent study in Sweden (81,88) but was not significantly elevated in a Danish cohort study of 3390 workers in a chemical plant manufacturing MCPA, dichlorprop, mecoprop, and 2,4-D, as well as other industrial chemicals and dyes (89).

Several case-referent studies suggest a weak link between chlorophenoxy herbicide use and NHL; however, concurrent exposure to other chemicals used in agriculture may contribute to this risk. In a study in Washington (576 cases of NHL), the relative risk increased from 1.1 for subjects with any past occupational exposure to chlorophenoxy herbicides, primarily 2,4-D and 2,4,5-T, to 1.7 for people occupationally exposed to such herbicides for at least 15 years (the minimum latency period) (87). In a
A case-referent study in Kansas (200 cases), farm herbicide use was marginally associated with NHL, with a relative risk of 1.4, which rose to 2.2 for farmers who had used chlorophenoxy herbicides at any time (almost all 2,4-D) and to 6.0 for those who had used unspecified herbicides for more than 20 days per year. The trend towards increasing risk with increasing number of days of use per year was highly significant (86). The risk for NHL (27 cases) was not elevated in a cohort of more than 20,000 Swedish pesticide applicators who applied MCPA, mecoprop, dichlorprop, and smaller amounts of 2,4-D (90). There was a slight nonsignificant trend towards a small increase in risk with increased number of years of exposure.

A nonsignificant excess in the relative risk for HD was seen in a cohort of 20,245 licensed pesticide applicators in Sweden who were exposed to MCPA, dichlorprop, mecoprop, and 2,4-D. There was a nonsignificant trend towards an increase in risk with the number of years since first licensing, with the risk increasing from 0.93 for those with 4 or fewer years to onset of disease to 2.2 for those with 10 or more years. The average follow-up time in this study was 13.9 years, a little less than the 15-20-year latency period reported for malignant lymphoma (90). In a study in Kansas, the relative risk for HD in people using herbicides (including chlorophenoxy compounds) was not elevated, nor was there evidence of a trend towards elevation of risk with increasing years of use of herbicides or frequency of use in days per year (86).

For the three end-points examined, the studies reviewed provide limited evidence that exposure to chlorophenoxy herbicides is associated with NHL rather than with HD or STS. With the exception of the early studies in Sweden (81,88), the associations seen in most studies were weak; there was usually a less than two-fold increase in relative risk for all three outcomes.

Reproductive effects

In cross-sectional epidemiological studies (91,92), long-term maternal exposure to low doses of 2,4,5-T were suspected of causing miscarriages and birth defects, particularly cleft palate and neural tube defects. In similar cross-sectional studies (93-95) and a cohort study on chemical workers (96), there was no correlation between exposure of either parent to 2,4,5-T and these effects (97,98).

15.31.7. Guideline values

Chlorophenoxy herbicides as a group, including 2,4-D and MCPA, have been classified by IARC in Group 2B (possibly carcinogenic to humans). However, the available data from studies on exposed populations and animals do not permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide. Therefore, drinking-water guidelines for these compounds are based on a threshold approach for other toxic effects.

Dichlorprop

Based on the 2-year study in rats (31), the NOAEL for renal toxicity is 100 mg/kg of diet, equal to 3.64 mg/kg of body weight per day. The TDI for dichlorprop was calculated to be 36.4 μg/kg of body weight by applying an uncertainty factor of 100 (for intra- and interspecies variation) to this NOAEL. With the allocation of 10% of the TDI to drinking-water, the guideline is 100 μg/litre (rounded figure).

2,4-DB

In a 2-year study in rats, the NOAEL for effects on body and organ weights, blood chemistry, and haematological parameters was determined to be 3 mg/kg of body weight per day (42). This value is similar to the NOAEL of 2.5 mg/kg of body weight per day obtained in the short-term study in beagle dogs and the NOAEL for hepatocytic hypertrophy of 5 mg/kg of body weight per day obtained in a 3-month study in rats (Department of National Health and Welfare, Canada, unpublished data, 1973). A TDI of 30 μg/kg of body weight was derived using an uncertainty factor of 100 (for intra- and interspecies variation).
With the allocation of 10% of the TDI to drinking-water, the guideline value is 90 µg/litre.

**2,4,5-T**

The NOAEL for reduced body weight gain, increased liver and kidney weights, and renal toxicity in a 2-year study in rats was 3 mg/kg of body weight per day (49). A NOAEL of 3 mg/kg of body weight per day for reproductive effects was also obtained in a three-generation study in rats (50). A TDI of 3 µg/kg of body weight was derived using the NOAEL from the 2-year rat study and an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the suggested association between 2,4,5-T and soft-tissue sarcoma and non-Hodgkin lymphoma in epidemiological studies). With the allocation of 10% of the TDI to drinking-water, the guideline for 2,4,5-T is 9 µg/litre.

**Fenoprop**

A NOAEL of 0.9 mg/kg of body weight per day for adverse effects on the liver was reported in a study in which beagle dogs were administered fenoprop in the diet for 2 years (29). A TDI of 3 µg/kg of body weight was derived using an uncertainty factor of 300 (100 for intra- and interspecies variation and 3 for limitations of the database). With an allocation of 10% of the TDI to drinking-water, the guideline value for fenoprop is 9 µg/litre.

**Mecoprop**

A NOAEL of 1 mg/kg of body weight per day for effects on kidney weight in 1- and 2-year studies in rats (65) was used with an uncertainty factor of 300 (100 for intra- and interspecies variation and 3 for limitations of the database) to derive a TDI of 3.33 µg/kg of body weight. With the allocation of 10% of the TDI to drinking-water, the guideline for mecoprop is 10 µg/litre (rounded figure).

**MCPB**

Currently available toxicological data are insufficient to be used as the basis for a guideline value for MCPB in drinking-water.

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