IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 147

Propachlor

Under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

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Environmental Health Criteria 147

PROPACHLOR

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World Health Organization
Geneva, 1993

The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone No. 7988400 or 7985850).

* * *

The proprietary information contained in this monograph cannot replace documentation for registration purposes, because the latter has to be closely linked to the source, the manufacturing route, and the purity/impurities of the substance to be registered. The data should be used in accordance with paragraph 82-84 and recommendations paragraph 90 of the Second FAO Government Consultation (FAO, 1982).

ENVIRONMENTAL HEALTH CRITERIA FOR PROPACHLOR

A WHO Task Group on Environmental Health Criteria for Propachlor met at the World Health Organization, Geneva, from 4 to 8 November 1991. Dr K.W. Jager, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director of the IPCS, and the three IPCS cooperating organizations (UNEP/ILO/WHO). The Group reviewed and revised the draft and made an evaluation of the risks for human health and the environment from exposure to propachlor.

The first draft was prepared by Dr L. Ivanova-Chemishanska of the Institute of Hygiene and Occupational Health, Sofia, Bulgaria, who also assisted in the preparation of the second draft, incorporating comments received following circulation of the first drafts to the IPCS Contact Points for Environmental Health Criteria monographs.

Dr K.W. Jager of the IPCS Central Unit was responsible for the scientific content of the monograph, and Dr P.G. Jenkins for the technical editing.

The fact that Monsanto Agrochemical Company, St Louis, USA, made available to the IPCS and the Task Group its proprietary toxicological information on their product is gratefully acknowledged. This allowed the Task Group to make its evaluation on a more complete data base.

The effort of all who helped in the preparation and finalization of the monograph is gratefully acknowledged.

ABBREVIATIONS

a.i.	active ingredient
AcP	acid phosphatase
ATPase	adenosine triphosphatase
CHO	Chinese hamster ovary
DMSO	dimethyl sulfoxide
GA	gibberillic acid
GGPT = GGT	gamma-glutamyltransferase
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
LAP	leucine aminopeptidase
LDH	lactate dehydrogenase
MAC	maximum allowable concentration
MAP	mercapturic acid pathway
mCi	millicurie
MQL	minimum quantifiable limit
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
OCT	ornithine carbamoyltransferase
ppb	parts per billion
ppm	parts per million
SAP = AP	alkaline phosphatase
SDH	succinate dehydroganase
SGOT = AST	aspartate aminotransferase
SGPT = ALT	alanine aminotransferase
UDS	unscheduled DNA synthesis
uv	ultraviolet
WP	wettable powder

1. SUMMARY AND EVALUATION

1.1 Identity, use pattern, physical and chemical properties, analytical methods

Propachlor is a pre-emergence and early post-emergence herbicide derived from acetanilide, and has been in use since 1965. The major formulations are as wettable powder, liquid flowable (suspension concentrate) and as granules. Its uses in agriculture include the control of annual grasses and some broad-leaved weeds in several crops including corn, sorghum, pumpkins, flax and flowers.

Propachlor is slightly soluble in water and readily soluble in most organic solvents. It has a low volatility, is non-flammable and is stable to ultraviolet radiation. The most practical method for analysis is gas chromatography with electron capture detection after suitable extraction and clean-up procedures.

1.2 Environmental transport, distribution and transformation

Propachlor is not known to photodegrade on soil surfaces. Volatilization of the compound occurs under windy conditions while the soil surface is still moist.

The adsorption of the compound to soil particles and organic matter is only moderate. This leads to the potential for leaching through the soil profile and into ground water. However, all studies show that this potential is unlikely to be realised in practice. Very high rainfall is required to move residues 30 cm down the soil profile. Most authors report that the great majority of residues remain within the upper 4 cm of soil. The characteristics of the soil greatly influence movement of the compound. Most leaching occurs in sandy soil with little organic matter.

Run-off of propachlor has been studied in both the laboratory and field. The organic matter in the soil reduced run-off from 7% to 1% of the applied herbicide in one study. Incorporation of propachlor into the soil also reduced loss through run-off (from 3% to 0.8% in one study).

By far the most significant factor in reducing propachlor levels in soil and water is degradation by microorganisms. Both bacteria

and fungi have been shown to be involved in breakdown of the compound. Few bacteria appear to be able to use propachlor as the sole carbon source. Bacteria capable of utilizing soil metabolites of propachlor have also been isolated.

The predominant metabolites formed in soil are water-soluble oxanilic and sulfonic acids. A large number of other metabolites can be formed, but these represent a small proportion of the total.

Propachlor disappears rapidly from soil, half-lives of up to 3 weeks having been reported. Most studies report almost complete degradation within less than 6 months. Environmental conditions affect the rate of degradation, which is favoured by high temperature and soil moisture content. Those studies reporting longer persistence of propachlor in soil were conducted under conditions of low temperature or dry soil. Adequate nutrient levels in soil are also necessary for degradation.

The conjugated *N*-isopropylaniline metabolite is much more persistent than the parent compound. Residues of this metabolite have been found up to 2 years after the application of propachlor experimentally at higher rates than would normally be used in agriculture.

Under normal conditions of use, propachlor is not expected to leach through soil to ground water and will not persist in soil. Exceptional conditions of low temperature or dryness will lead to greater persistence of propachlor and its metabolites.

Under normal conditions, propachlor does not photodegrade significantly in water. In the presence of photosensitizers, photodegradation may take place. Propachlor is hydrolytically stable. Volatilization from water is unlikely because of the high water solubility and low vapour pressure of the compound.

As in soil, the major route of loss of propachlor from water is biotic degradation. The rate of loss of propachlor from water is, therefore, dependent on the microbial population. A study in water with few bacteria present yielded a half-life of about 5 months. Ring cleavage did not occur within six weeks in another study. Laboratory model ecosystem studies showed almost complete degradation of propachlor within 33 days.

In several studies on different plant species, propachlor was shown to be rapidly metabolized in both intact plants and excized

plant tissues. The metabolic pathways were similar in all plants studied, at least for the first 6 to 24 h, producing water-soluble metabolites. No metabolic breakdown of the *N*-isopropylaniline moiety was observed. Only a very small proportion (< 1% in one study) of the metabolites was found in the fruit of the plants; the great majority was in the roots and foliage. The major metabolites produced in plants are identical with those produced in soil. Uptake of these metabolites from soil is known to take place and it is uncertain in some studies whether measured metabolites derive from the plant or the soil.

Although the octanol/water partition coefficient suggests a moderate potential for bioaccumulation, studies show that propachlor neither bioconcentrates nor biomagnifies in organisms.

1.3 Environmental levels and human exposure

Reported measurements of air concentrations of propachlor during application are few and inadequate.

Concentrations in surface and ground water in the USA were consistently low, the maxima being at 10 μg/litre in surface and 0.12 μg/litre in ground water. The highest water concentration recorded in a run-off study was 46 μg/litre.

Propachlor residues in food are usually below the detection limit of the analytical method (0.005 mg/kg). Experimental studies have identified residues in the order of 0.05 mg/kg in tomatoes, peppers, onions and cabbage.

Measurements of propachlor in the air of the working zone of tractor drivers applying the compound ranged between 0.1 and 3.7 mg/m^3.

1.4 Kinetics and metabolism

Propachlor can be absorbed into mammals through the respiratory and gastrointestinal tract as well as through the skin. It does not accumulate in the body. After 48 h it is not detectable in the organism.

Most animal species (rats, pigs, chickens) metabolize propachlor through the mercapturic acid pathway (MAP). Cysteine conjugates are formed by glutathione conjugation and this conjugate has been proposed as an intermediate in the metabolic formation of

mercapturic acids. Bacterial C-S lyase participates in the further metabolism of the cysteine conjugate of propachlor and in the formation of the final methylsulfonyl-containing metabolites, which are mainly excreted in the urine (68% of the dose of propachlor), and insoluble residues, which are excreted in the faeces (19%). The propachlor C-S lyase is not active in germ-free rats.

Studies showed some differences in metabolism between the rat and pig. The bile is the major route of elimination of MAP metabolites in the rat, but it is has been proved that an extrabiliary route of metabolism exists in the pig.

Metabolic studies on calves showed that they may be unable to form mercapturic acids from glutathione conjugates, which may make them more susceptible to poisoning.

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

Propachlor is slightly toxic in acute oral exposure (the LD_{50} in rats ranges from 950 to 2176 mg/kg body weight). Signs of acute intoxication are predominantly central nervous system effects (excitement and convulsion followed by depression). The acute inhalation toxicity in rodents is low (LC_{50} = 1.0 mg/litre). Propachlor caused severe irritation effects on eyes and skin.

Propachlor has been tested in short- and long-term exposure studies on rats, mice and dogs. The liver and kidneys are the target organs. In dogs, the no-observed-adverse-effect level (NOAEL) was 45 mg/kg body weight in a 3-month dietary exposure study. In a one-year study on dogs, the NOAEL was 9 mg/kg body weight (250 ppm in diet). The no-observed-effect level (NOEL) in a 24-month dietary exposure study on rats was 50 mg/kg diet (2.6 mg/kg body weight). In an 18-month dietary study in mice, the NOEL was 1.6 mg/kg body weight (10 ppm).

Propachlor was not found to be carcinogenic in mice and rats. It showed a negative mutagenic response in most of the mammalian test systems and positive results in a few assays. The experimental data available provide insufficient evidence of the mutagenic potential.

When tested as a single dose (675 mg/kg) in rats and mice, propachlor showed positive evidence of embryotoxicity. Embrytoxic effects were also observed in repeated dose regimens

(35.7-270 mg/kg). However, in another rat study using a dose range of 20-200 mg/kg, no embryotoxicity was observed.

At levels of 12 and 60 mg/kg body weight, propachlor (wettable powder) resulted in a decrease in protein content and an increase in ATPase and 5-nucleotidase activity in rat testis homogenate and degenerative changes in the testes. In a two-generation reproduction study there was no definite evidence of adverse effects.

1.6 Effects on humans

A few cases of contact and allergic dermatitis of farmers and production workers exposed to propachlor (Ramrod and Satecid) have been reported. Patch tests were carried out among some of them, revealing a positive patch test reaction, irritation reaction or mono- and bi-valent hypersensitivity.

There have been no reports of symptoms or diseases either among occupationally exposed humans or the general population other than the few reports of its effects on the skin of occupationally exposed workers.

1.7 Effects on organisms in the environment

In studies on soil microorganisms, nitrifying bacteria were the most sensitive group to the inhibitory effects of propachlor, their numbers being reduced by a factor of 3 to 4 after the application of 8 to 10 kg propachlor/ha. Cellulose-decomposing bacteria were the least sensitive. High adsorption to clay particles in soil and high temperature both reduce the inhibitory effects.

A 96-h EC_{50} of 0.02 mg/litre for growth and a no-observed-effect concentration (NOEC) of 0.01 mg/litre have been reported for the alga *Selenastrum capricornutum*. A second study using a formulation and conducted over 72 h suggested substantially less hazard for the same organism.

LC_{50} values of 7.8 and 6.9 mg/litre have been reported for the water flea *Daphnia magna* and a NOEC of < 5.6 mg/litre. The NOEC for reproduction was 0.097 mg/litre. LC_{50} values of 0.79 and 1.8 mg/litre have been reported for two species of midge larvae.

The 96-h LC_{50} for rainbow trout is 0.17 mg/litre and the NOEC in a 21-day study was 0.019 mg/litre.

Propachlor is considered to be moderately to highly toxic to aquatic organisms.

Propachlor is not toxic to earthworms at exposure concentrations in soil expected from normal use (the NOEC is 100 mg/kg soil). The contact LD_{50} for honey bees (311 μg/bee) shows that propachlor will not pose a hazard to these insects. Some beneficial parasitic insects have been reported to be adversely affected by propachlor in laboratory and field studies.

Propachlor is more toxic to birds when administered via the stomach than when fed in the diet. Acute LD_{50} values range between 137 and 735 mg/kg body weight for different bird species. The LC_{50} values from dietary exposure exceed 5620 mg/kg diet in birds.

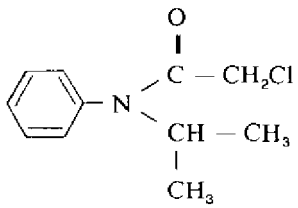
Propachlor does not pose a hazard to birds in the field, even with the granular formulation.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

2.1 Identity

Common name: Propachlor

Chemical structure



Chemical formula: $C_{11}H_{14}ClNO$

Common synonyms and trade names: Ramrod, Acylide, Bexton (discontinued by Dow Chemical Company), Niticid, Satecid

CAS chemical name: 2-chloro-*N*-(1-methylethyl)-*N*-phenyl acetamide

IUPAC name: 2-chloro-*N*-isopropylacetanilide (formerly alpha-chloro-*N*-isopropylacetanilide)

CAS registry number: 1918-16-7

RTECS registry number: AE1575000

Propachlor is available as a technical material containing 93% active ingredient for formulation of propachlor end-use products. It is available in the form of granules (200 g active ingredient/kg), wettable powder (WP, 650 g active ingredient/kg) and as a liquid flowable formulation (suspension concentrate), among others. Mixtures with other herbicides, e.g., atrazine and propazine are also used.

2.2 Physical and chemical properties

Some of the physical and chemical properties of propachlor are given in Table 1.

Table 1. Some physical and chemical properties of propachlor

Physical state	solid
Colour	tan
Relative molecular mass	211.7
Melting point (°C)	77
Boiling point (°C) at 0.03 mmHg	110
Decomposition (°C)	> 170
Vapour pressure (25 °C)	103 mPa
Solubility in water (20 °C)	580 mg/litre
(25 °C)	613 mg/litre
Solubility in organic solvents	readily soluble in most organic solvents except aliphatic hydrocarbons:
acetone	448 g/kg
benzene	737 g/kg
chloroform	602 g/kg
ethanol	408 g/kg
xylene	239 g/kg
Log K_{ow}	1.62-2.30

It is non-flammable and stable to ultraviolet radiation.

2.3 Conversion factors

At 25 °C 1 mg/m^3 = 8.802 ppm
1 ppm = 0.1136 mg/m^3

2.4 Analytical methods

The analytical methods described in the literature, which are based on different types of determination of propachlor in different media, are given in Table 2.

Table 2. Analytical methods for the determination of propachlor and metabolites

Sample type	Method of detection	Extraction and clean-up	Detection limit	Reference
Soil and plants	thin-layer chromatography	2-h extraction with chloroform	0.02-0.04 mg/kg	Kofman & Nishko (1984)
Soil and plants	gas chromatography with electron-capture detection	extraction with benzene; clean-up by partition with hexane-acetonitrile followed by column chromatography (Florisil)	0.004-0.005 mg/kg	Batinova (1981)
Soil	gas chromatography with electron-capture detection	acetone extraction followed by alkane hydrolysis, steam distillation and concentration of anilines in toluene	0.01 mg/kg; recoveries at residual levels are generally better than 80%	Caverly & Denney (1978)
Soil	gas liquid chromatography with flame-ionization detection	extraction with isopropanol and benzene; column chromatography (Florisil)	< 0.05 mg/kg	Markus & Puma (1973)
Immature plants	gas-liquid chromatography with flame-ionization detection	extraction with isopropanol; column chromatography (Florisil)	< 0.05 mg/kg	Markus & Puma (1973)

Table 2 (contd).

Sample type	Method of detection	Extraction and clean-up	Detection limit	Reference
Mature grain	gas-liquid chromatography with flame-ionization detection	extraction with acetonitrile; column chromatography (Florisil)	< 0.05 mg/kg	Markus & Puma (1973)
Cabbage	gas chromatography with NP detection	extraction with acetone followed by alkaline hydrolysis to *N*-isopropyl-aniline; steam distillation and extraction with toluene	0.06 mg/kg (fresh weight)	Warholic et al. (1983)
Industrial and municipal waste water	gas chromatography with electron-capture detection	extraction with methylene chloride; clean-up on a Florisil column	1 ng/litre	Pressley & Longbottom (1982)
Urine metabolites of propachlor (glutathione conjugates)	gas or liquid chromatography and mass spectrometry	fractionation with lipophilic ion exchangers (Lipidex 1000, Lipidex DEAP SP-LH-20 and Sep pack C_{18})	not given	Sjovall et al. (1983)

High-pressure liquid chromatography with radioactive detection or liquid scintillation has been used to purify the metabolites from ^{14}C-labelled propachlor in several biological media, including egg yolk, egg white, edible tissues and excreta of laying hens, after extraction with organic solvents. The metabolites were characterized by gas chromatography with radioactive detection mass spectrometry (Bleeke et al., 1987). With liquid scintillation detection, the minimum quantifiable limit (MQL) was 0.01 to 0005 ppm.

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Production and uses

Propachlor was developed by the Monsanto Chemical Company and commercially introduced in 1965. Technical propachlor is produced in the USA by Monsanto and in Germany by BASF. There are other manufacturers of technical propachlor.

Propachlor is prepared by the reaction of chloracetyl chloride and *N*-isopropylaniline.

It is a pre-emergence, pre-planting (incorporated) or early post-emergence herbicide effective against annual grasses and some broad-leaved weeds (Worthing & Hance, 1991). It is used on field corn, hybrid seed corn, silage corn, grain sorghum (milo), green peas, soybeans, flax, pumpkins and flowers. In 1971, 10 000 tonnes were produced (US EPA, 1984a), but a more recent estimate of annual use in the USA is 1800 tonnes.

3.2 Methods and rates of application

Application rates range from 4 to 6 kg active ingredient in 150-300 litres of water per ha (6-9 kg wettable powder formulation/ha) in pre-emergence use. Some tests indicate that early post-emergence applications are equally effective for weed control. The best response occurred when broad-leaved weeds were between the cotyledonous stage and the 2½-leaf stage and when grassy weeds were up to the one-leaf stage.

Irrigation following application improves activity, particularly under dry soil conditions. The duration of weed control ranges from 4 to 6 weeks, depending on the soil structure and organic content (Humburg et al., 1989).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

4.1.1 Soil

The fate and transport of propachlor in soil has been well studied. The principal aim has been to determine the rate and products of degradation, persistence, environmental factors and organisms participating in the biodegradation, and the conditions under which degradation takes place.

4.1.1.1 Abiotic factors

Beestman & Deming (1974) found that leaching did not contribute to dissipation since no residues were found below the upper 4-cm layer. The weak leaching ability was related to the high adsorption of propachlor by soil. The ultraviolet absorption spectrum of propachlor reveals no absorption at wavelengths longer than 280 nm. On the basis of these data it was suggested that photodecomposition of soil-applied propachlor would not be significant. Rapid herbicide volatilization occurred under windy conditions during the period that exposed soil surfaces remain moist.

In a study by Nesterova et al. (1980), propachlor was applied, under dry weather conditions, at a rate of 7 kg/ha for 4 consecutive years. The residues of propachlor in the soil were measured up to 4 weeks following the application. On the 5th day, residues were found in the upper layers (0-10 cm), and on the 15th day, after abundant rain (74 mm), they had reached 0-30 cm. There was rapid biodegradation, mainly in the first 5 days, followed by reduced degradation over the next 10 days. Between the 15th and 30th day, no residues were detected.

The mobility of ^{14}C-propachlor in the soil was investigated by Brightwell et al. (1981) by determining its leaching as well as its adsorption coefficient and desorption behaviour. Results were very variable and depended on soil type. With a sandy loam, 89.5% of the ^{14}C activity applied leached through laboratory soil columns, whereas only 5.4% leached through silty clay loam. A high organic matter content reduced the leachability of propachlor. Most of the radioactivity represented the parent

compound. Propachlor was adsorbed only moderately, although the equivalent of 50 cm of rain was needed to desorb 40 to 70% of the activity previously bound to soil to a depth of 30 cm in the profile.

The mobility of propachlor in soil was the object of a study carried out by Ritter et al. (1973). The diffusion coefficient of propachlor in a silt loam soil was determined and was compared with the coefficients of two other pesticides, atrazine and diazinone. It was found that propachlor had the highest solubility and the largest diffusion coefficient, which allowed it to move rapidly in the soil. The movement increased with the temperature and moisture contents.

The run-off losses of propachlor have been studied by Baker & Laflen (1979), Baker (1980) and Baker et al. (1982). Rainfall simulation was used by Baker et al. (1982) to determine the effects of corn residue on herbicide run-off losses from the soil. Propachlor was applied to plots with 0, 375, 750 and 1500 kg corn residue per ha, and a 2-h rainfall of 127 mm was simulated. For plots with no corn residue, the average time to run-off was 11 min; run-off was 63 mm, soil loss 11 tonnes/ha, and herbicide loss 7% of the amount applied. Increased corn residue amounts increased time to run-off and decreased run-off, erosion and herbicide losses. Time to run-off for the largest corn residue amount was 30 min, run-off 18 mm, soil loss 1 tonne/ha, and herbicide loss 1%. At least 84% of the herbicide losses were in the dissolved phase. Herbicide placement had little or no effect on the concentrations of herbicide in run-off water and sediment. Herbicide concentrations in water and sediment were negatively correlated with time to run-off.

The effects of incorporation and surface application on run-off losses of propachlor were determined by measuring losses in water and sediment from small plots during 122 mm of simulated rainfall (Baker & Laflen, 1979). Losses of propachlor that was surface-applied to plots were 3%, whereas losses from plots where the herbicide was incorporated by disking were only 0.8%. Incorporation of herbicide has the potential to decrease run-off losses and may be considered the best application method.

In a laboratory study, propachlor was applied at rates of 0.4 and 1.8 kg/ha to corn (*Zea mays*) residue, which in turn was subjected to simulated rainfall (Martin et al., 1978). Initial concentrations in wash-off water were high (9 mg/litre for the high application

rate), but this decreased rapidly with time. The mass balance showed that most of the applied dose was washed off and little was retained by the corn residue. Unexplained losses indicated the possibility of volatilization occurring between application of herbicide and application of wash-off water about 12 h later.

Gustafson (1989) described a method combining persistence and mobility parameters to assess the potential for leaching and contamination of ground water by propachlor. The author concluded that propachlor was unlikely to leach through the soil into subsoil water and ground water.

4.1.1.2 *Biotic factors*

Beestman & Deming (1974) carried out a large study to determine the dissipation rate under laboratory and field conditions from Ray silt and Wabash silty clay soils and to quantify the contributions of microbial decomposition, chemical breakdown, volatilization and leaching. Dissipation followed first-order kinetics with half-lives ranging from 2 to 14 days. In moist Ray silt the half-life of propachlor was 4.5 days. The important role of microbial degradation was clearly established. Dissipation from sterilized soil was 50 times slower ($T_{½}$ = 141–151 days) than from unsterilized soil under identical conditions.

Rankov & Velev (1977) conducted a model study over 120 days with 10 microscopic fungi from the genera *Penicillium*, *Aspergillus*, *Fusarium* and *Trichoderma* concerning the degradation and detoxication of propachlor in alluvial meadow soil at 28 °C and 65% soil humidity. The results confirmed the important role of microscopic fungi in increasing the rate of propachlor degradation and detoxication.

Villarreal et al. (1991) enriched microbial cultures from a pesticide disposal site to identify the range of metabolic capacity for propachlor and its metabolites and the species involved in breakdown of the compound. A single strain, corresponding most closely to the genus *Moraxella*, could grow on propachlor as its sole carbon source releasing a metabolite (2-chloro-*N*-isopropyl-acetamide) into the medium. A second strain, corresponding to the genus *Xanthobacter* grew on the metabolite. The *Moraxella* strain appears to use the aromatic carbon atoms of the propachlor for growth since there was induction of catechol 2,3-oxygenase activity in the cells and the growth rate was sustainable only from this source.

Novick et al. (1986) showed that suspensions of soil treated in the field with propachlor could mineralize 16-61% and 0.6-63% of ring-labelled propachlor in 30 days at propachlor concentrations of 0.025 and 10 mg/litre, respectively. A mixture of two bacteria mineralized 57.6% of propachlor within 52.5 h, producing *N*-isopropylaniline as a metabolite.

4.1.1.3 Metabolites

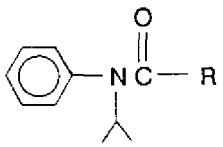
N-isopropylaniline, *N*-isopropylacetanilide, *N*-(1-hydroxyisopropyl)-acetanilide and *N*-isopropyl-2-acetoxyacetanilide are formed as metabolites of propachlor in soil (Lee et al., 1982). Frank et al. (1977) demonstrated the existence of a longer-lasting conjugated degradation product of propachlor in onions and in organic soils following soil application. This was conjugated *N*-isopropylaniline, which could be found in soil up to 2 years after application.

An extensive study on the environmental and metabolic fate of propachlor was conducted by Brightwell et al. (1981). A variety of soil metabolites was identified, the most significant resulting from the modification of the C-2 carbon to yield water-soluble oxanilic and sulfonic acids. The soil metabolism studies demonstrated the predominant proportion of the water-soluble metabolites, i.e. [(1-methylethyl) phenylamino] oxoacetic acid (IV), 2-[(1-methylethyl) phenylamino]-2-oxoethanesulfonic acid (V) and {{[(methylethyl) phenylamino] acetyl}sulfinyl}acetic acid (VI). These metabolites accounted for 25, 17, and 6% of the applied ^{14}C activity, respectively, at different sampling points during the studies. There was a decline in the level of these metabolites with time (Fig. 1).

In addition, several organic soluble metabolites were isolated and identified; these included *N*-(1-methylethyl)-2-(methylsulfinyl)-*N*-phenylacetamide (VII), *N*-(1-methylethyl)-2(methyl sulfonyl)-*N*-phenylacetamide and 2-hydroxy-*N*-(1-methylethyl)-*N*-phenylacetamide (II). These accounted for no more than 6% of the applied activity. The degradation products observed in the anaerobic soil metabolism study were comparable to those observed under aerobic conditions, but the rate of degradation in aerobic conditions was higher.

Lamoureux & Rusness (1989) studied the metabolism of propachlor and the cysteine conjugate of propachlor in sandy loam soil. Both compounds were metabolized at similar rates to three

major products: *N*-isopropyloxanilic acid, 2-sulfo-*N*-isopropylacetanilide and 2-(sulfinylmethylenecarboxy)-*N*-isopropylacetanilide.



I. R = CH_2Cl
2-chloro-*N*-(1-methylethyl)-*N*-phenylacetamide = propachlor

II. R = CH_2OH
2-hydroxy-*N*-(1-methylethyl)-*N*-phenylacetamide

III. R = CH_3
N-(1-methylethyl)-*N*-phenylacetamide

IV. R = $-\overset{O}{\overset{\|}{C}}OH$
[(1-methylethyl)phenylamino]oxoacetic acid

V. R = CH_2SO_3H
2-[(1-methylethyl)phenylamino]-2-oxoethanesulfonic acid

VI. R = $CH_2\overset{O}{\overset{\|}{S}}CH_2\overset{O}{\overset{\|}{C}}OH$
{{[(methylethyl)phenylamino]acetyl}sulfinyl}-acetic acid

VII. R = $CH_2\overset{O}{\overset{\|}{S}}CH_3$
N-(1-methylethyl)-2-(methylsulfinyl)-*N*-phenylacetamide

Fig. 1. Structures of propachlor degradation products.

4.1.1.4 Persistence

Fletcher & Kirkwood (1982) reported a half-life of 2-3 weeks for propachlor. Free propachlor disappeared rapidly in soil treated by Ritter et al. (1973); in 21-28 days residues of free propachlor declined 72-80%. In earlier laboratory studies and field bioassays carried out by Menges & Tamez (1973), the soil persistence (> 90% degradation) was found to be less than 6 months. According to Melnikov et al. (1985) and Zhukova & Shirko (1979), the period of propachlor degradation in soil to non-toxic products is about 2 months. The presence of an alkyl group attached to the nitrogen atom in its molecule prevents its decomposition to aniline or to azobenzolic residues, which could later be transferred into tetrachlorazobenzene (Panshina, 1985). Propachlor applied at 4-8 kg/ha was detoxified in peat soil within 59-63 days (Vasilev, 1982). When it was applied at 6.5, 9 and 11 kg/ha, it was still detectable after 113 days in two types of soil in the Voronezh and Krasnodar regions of the former USSR (Kolesnikov et al., 1980). The longer persistence determined in this study might be connected with the climatic conditions, particularly the low temperatures. Roberts et al. (1978) and Balinova (1981) confirmed that propachlor is rapidly decomposed in soil.

Field studies evaluating the degradation of propachlor in soil showed that 70 days after application, propachlor was detectable in insignificant quantities (0.04 mg/kg, i.e. 2% of the dose applied). Degradation was slower in dry than humid weather (Zhukova & Shirko, 1979) (Table 3). The conclusions of the authors were that degradation in soil is rapid and there is no possibility of propachlor accumulation in crops.

Table 3. Dynamics of dissipation of propachlor in soil (average data for 1974-1976)[a]

Dose application (kg propachlor/ha)	After 10th day		On 30th day		On 50th day		On 70th day	
	mg/kg	%[b]	mg/kg	%[b]	mg/kg	%[b]	mg/kg	%[b]
6	1.73	86.4	0.95	42.8	0.10	5.2	0.04	2
8	2.44	92.5	1.55	58.3	0.20	7.8	0.04	2
10	3.14	94.2	2.53	76.0	0.40	12.0	0.04	2

[a] From: Zhukova & Shirko (1979)
[b] Percentage of dose applied

In a study by Frank et al. (1977), soil with high organic matter content was treated with 19 kg propachlor/ha. The treatment times and rates are given in Table 4. Soil samples were collected to a depth of 20 cm and analysed. Residues of the conjugated metabolite *N*-isopropylaniline of up to 3.7 mg/kg soil were detected 2 years after the application. They were released from soil by hydrolysis, indicating the presence of active bonding sites for the metabolite in the soil. The authors concluded that using propachlor in successive years led to accumulation of long-lasting conjugated *N*-isopropylaniline. Applications made once every 3 years, however, did not lead to such accumulation and they recommended this type of application.

Table 4. Residues of conjugated *N*-isopropylaniline in organic soil treated with propachlor in 1971, 1972 and 1975[a].

Year	Time of application	Rate of application (kg/ha)[b]	*N*-isopropylaniline residues in oven-dried soil (mg/kg)
1971	May and June	9 + 10	not analysed
1972	untreated	none	3.67
	May, July, August	6.7 + 3.4 + 3.4	7.70
	May, July, August	6.7 + 6.7 + 6.7	9.47
1975	May and June	6.7 + 6.7	3.16

[a] From: Frank et al. (1977)
[b] Soil samples were collected in May 1973 and April 1976 and analysed in January and April 1976, respectively.

US EPA (1984b) re-evaluated the existing data concerning some environmental aspects of propachlor. It was concluded that microbes were the primary factor in its breakdown in soil and that its loss from photodecomposition and/or volatilization was low. Although this earlier assessment suggested a potential for propachlor to contaminate ground water, a later assessment (US EPA, 1988) concluded that "the rapid degradation of low levels of propachlor in soil is expected to result in a low potential for groundwater contamination by propachlor".

4.1.1.5 Environmental conditions affecting distribution and breakdown

Walker & Brown (1982, 1985) carried out laboratory studies and field trials in parallel. They found first-order kinetics dissipation of propachlor and confirmed the results of Beestman & Deming (1974). They also described a clear temperature dependence: an increase in temperature of 10 °C reduced the half-life by a factor of between 1.9 and 2.5. Soil moisture also influenced degradation: slower rates of loss were found in drier soil. The half-life in soil with a moisture content of 6% was about twice as long as at 15% (Table 5). In general, the time of persistence in the field was comparable to that measured in laboratory studies. The half-life of propachlor varied from 4 to 22 days (Table 5).

Table 5. Half-life for propachlor degradation (days)[a]

Temperature (°C)	25	25	25	25	15	5
Moisture (%)	6	9	12	15	12	12
Propachlor	7.7	4.6	4.2	3.7	9.2	21.7

[a] From: Walker & Brown (1985)

The persistence of propachlor in soil as a result of all microbial, chemical and physical processes has been studied by Zimdahl & Clark (1982). They measured the half-life of propachlor in clay loam and sandy loam soils in the laboratory, using different temperature and moisture conditions (Table 6). An increase in temperature (from 10 to 30 °C) and moisture content (from 20 to 80%) shortened the half-life.

Vasilev (1982) confirmed the importance of meterological conditions, type of soil, and rate and period of application on the degradation in soil. In dry weather, degradation took longer than in humid conditions. Based on field experiments where soil was treated with propachlor and carrots were then planted, the author reported the following residues (measured at the moment of harvest in the soil layer 0-20 cm) in soil: at an application rate of 4 kg/ha the propachlor residues were 0.05 mg/kg; at 6 kg/ha they were 0.15 mg/kg; and at 8 kg/ha they were 0.2 mg/kg.

Table 6. Half-lives of propachlor in clay loam and sandy loam as determined by bioassay[a]

Storage conditions		Half-life (days)	
Temperature (°C)	Soil moisture (%)	Sandy loam	Clay loam
10	50	16.7	14.3
20	50	3.3	5.3
30	50	1.9	1
20	20	23.1	21.5
20	50	3.3	5.3
20	80	3.3	4.1

[a] From: Zimdahl & Clark (1982)

Shirko & Belova (1982) found that residues of propachlor in soil and plants depended on the nitrogen and potassium content of the soil. At the moment of harvesting, no residues of propachlor were detected in soil after application at a rate of 4.5-6.5 kg/ha. According to the authors, a better supply of plants with nutrients (in this case, nitrogen and potassium fertilizers) leads to more intense detoxification and degradation of the herbicide and, conversely, an insufficiency delays the detoxification processes and leads to the accumulation of residues.

4.1.2 Water

Photodegradation of propachlor in aqueous media was studied by Tanaka et al. (1981) under laboratory conditions. They used a 10-ml sample with propachlor concentrations ranging up to 100 mg/litre, and the sample was irradiated for 135 min with a 300-nm sunlight lamp. Very weak photolysis was registered; by the end of the study only 1% of herbicide had been lost. Addition of a commercial surfactant (2% heterogeneous non-ionic Tergitol TMN, acting as photosensitizer) allowed 37% of propachlor to be photodegraded. It is difficult to make conclusions on this study because of certain deficiencies. The use of a commercial formulation in such studies should be avoided since some of the constituents may cause indirect photochemical reactions. No

mention was made in the report of the purity of the compound studied. The test should preferably be carried out at constant temperature. The lack of data concerning the intensity of the irradiation source (US EPA, 1984a) does not allow any extrapolation of these data to the environment.

Rejtö et al. (1984) investigated the effects of ultraviolet irradiation of propachlor solutions and found that 5 h of irradiation led to 80% decomposition. The three photodecomposition products identified were: *N*-isopropyloxindole, *N*-isopropyl-3-hydroxyoxindole and a spiro compound. Irradiation of a solution of propachlor with visible light for 12 h led to almost complete decomposition in the presence of riboflavin as a photosensitizer. The photodecomposition products after visible light irradiation were found to be non-phytotoxic.

Monsanto (1987) demonstrated that propachlor is hydrolytically stable.

Volatilization of propachlor from aqueous media is of limited significance because of the high solubility in water and relatively low vapour pressure of the compound. In agreement with Henry's constant, the loss of propachlor by sorption and sedimentation in water bodies does not appear to be very significant (US EPA, 1984a).

The role of microbial biodegradation appears to be of major significance in water as well as in soil. Novick & Alexander (1985) studied the metabolism of low concentrations (10 µg/litre) of propachlor in sewage and lake water. They found that under aerobic conditions microbial populations from sewage and lake waters were not able to mineralize the carbon ring of propachlor in six weeks. However, propachlor was extensively metabolized, the products obtained were organic, and they were found to accumulate in the environment. In a parallel study, it was found that aniline was readily cleaved under similar conditions, indicating rapid mineralization of this compound. It was concluded that structural characteristics of propachlor, other than the ring, account for the mineralization of the compound. The presence of the three substituents on the nitrogen atom in propachlor may be the reason for its persistence. Steen & Collette (1989) determined microbial transformation rate constants for seven amides in natural pond water. A second order mathematical rate expression served to describe propachlor degradation, and a value of 1.1×10^{-9} litres/organism per h was calculated. Brightwell

et al. (1981) presented data showing slow degradation of propachlor in lake water under aerobic conditions. After 30 days, 84.5% of the propachlor remained unchanged; under these conditions a half-life of about 5 months would be expected. The low rate of metabolism was due to a low level of microorganisms. Yu et al. (1975) studied the degradation of propachlor in water using a model ecosystem. An aquarium with 7-day-old sorghum plants was used with the addition of 50 μCi of ^{14}C ring-labelled propachlor. By the end of the 33-day experimental period, 7 degradation products in water were determined by thin-layer chromatography but were not identified. At that time only 0.4% of the radioactivity of the dose applied remained in the water.

4.1.3 Plants

The metabolism of propachlor in corn seedlings and in excized leaves of corn, sorghum, sugar cane and barley was studied by Lamoureux et al. (1971). Metabolism was rapid and similar in all mentioned plant species during the first 6-24 h following treatment. At least 3 water-soluble metabolites were produced in each species during this period. Two of these metabolites were isolated; the first one was identified as the glutathione conjugate of propachlor (compound I) and the second one appeared to be the gamma-glutamylcysteine conjugate (compound II). The primary mode of metabolism is a nucleophilic displacement of the alpha-chloro group of propachlor by the sulfhydryl group of a peptide. The metabolic reactions of propachlor proceed non-enzymatically *in vitro*, and the *in vivo* reaction may be enzymatic and/or non-enzymatic. The high percentage of propachlor converted to compounds I and II in corn seedlings during the first 18 h following treatment indicates that the reaction of propachlor with glutathione and/or gamma-glutamylcysteine is quite specific. This would be expected if the reaction is enzymatic. Some glutathione and gamma-glutamylcysteine conjugates in plants may be end-products, but, in the case of propachlor, these metabolites are transient intermediates. Further studies are needed to establish the final steps (Lamoureux et al., 1971).

Pantano & Anderson (1987) studied the metabolism of propachlor in sorghum (milo). Sorghum seeds were planted in soil treated with ^{14}C ring-labelled propachlor at a rate of 3.3 kg/ha and grown to maturity in a greenhouse. Following senescence, plants were separated into various anatomical parts, freeze-dried and analysed for activity. The uptake of ^{14}C in the foliage and grain was 9.5 and 0.5 mg/kg dry weight, respectively. Four metabolites

were identified in the foliage extract; these represented 66.5% of the metabolites in foliage. The four metabolites were [(*N*-isopropyl) phenylamino]oxoacetic acid, {{[(*N*-isopropyl)-phenylamino]acetyl}sulfinyl}lactic acid, {{[(*N*-isopropyl)phenylamino] acetyl}sulfinyl}acetic acid and 2-[(*N*-isopropyl)phenylamino]-2-oxoethanesulfonic acid. In addition, other metabolites found at low levels in the foliage extract were characterized. Freeze-dried sorghum grain contained only 0.5 mg/kg of ^{14}C activity and only one metabolite was identified (the first compound mentioned above). This metabolite constituted at least 24.9% of the activity in grain. In all of the major metabolites identified in this study, no modification of the *N*-isopropylaniline moiety was observed. On the basis of metabolites identified in this study and known pathways for the metabolic transformations of related chloroacetamides, a scheme for the metabolic fate of propachlor in sorghum plants was postulated by the authors. The biotransformations include: 1) displacement of the chlorine by an oxygen-containing nucleophile followed by oxidation, and 2) conjugation with glutathione followed by further metabolic modification of this conjugate.

Lamoureux & Rusness (1989) studied the metabolism of propachlor in soybean and found that it was rapidly metabolized to homoglutathione conjugate in roots and foliage. This conjugate was rapidly metabolized to the cysteine conjugate and then slowly converted to a variety of other metabolites; four of these were present up to 72 days after application of propachlor. These four were malonylcysteine, malonylcysteine *S*-oxide, 3-sulfinyllactic acid and *O*-malonyl glucoside conjugates of propachlor. Less than 1% of metabolites was isolated from beans or pods, the great majority being in roots and foliage. The major metabolites found in plants were the same as those produced in soil. The authors suggested that it is difficult to differentiate between metabolites formed in the plant and those taken up from soil as to the relative importance of the two sites of metabolic degradation.

4.2 Bioaccumulation and biomagnification

The two published values for the log octanol/water partition coefficient (log K_{ow}) of propachlor, i.e. 1.62 and 2.3 (US EPA, 1984b, 1988), indicate a moderate potential for bioaccumulation.

Barrows & Macek (1974) used bluegill sunfish exposed to ^{14}C-labelled propachlor in a continuous-flow experiment in order to assess the potential for the compound to bioconcentrate in aquatic

organisms. The fish were exposed for 35 days to a mean ^{14}C-propachlor concentration of either 0.54 mg/litre (high level) or 0.012 mg/litre (low level) in the water. Analysis of the fish tissues indicated bioconcentration factors (BCFs) in the edible tissue of 34 and 22 for the high and low levels, respectively, and in the non-edible tissue of 22 and 20. When the fish were placed in clean water the activity was rapidly eliminated from the non-edible portion of the fish and at a somewhat slower rate from the edible tissue. Because of the polar, water-soluble nature of the soil metabolites (section 4.1.1), they would be less likely to bioconcentrate in aquatic organisms. The results of a static study on catfish by Malik (1982) showed that BCFs for both edible and non-edible tissues were 0.23 and that the low level of accumulated activity was eliminated rapidly when the fish were placed in clean water.

Yu et al. (1975) studied ^{14}C-propachlor in a model ecosystem containing seven species. There was no indication of either bioconcentration or biomagnification; total radioactivity declined from 0.21 to 0.015 mg propachlor/kg through the seven stages of the food chain.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

The application of propachlor as a herbicide in plant protection results in its presence in air, soil and water. It is taken up from the soil into plants through the root system.

5.1.1 Air

Propachlor application resulted in its presence in the ambient air 300 m away from the treated field at concentrations ranging from 0.02-0.6 mg/m^3 (Panshina, 1976). No details on the analytical method or quantity of propachlor sprayed were given in this report.

5.1.2 Water

Propachlor was found in 34 of 1690 surface water samples analysed in the USA (US EPA, 1988). Samples of surface water were collected at 475 locations and groundwater samples at 94 locations. The compound was detected in eight different states. The maximum concentration found was 10 μg/litre in surface water and 0.12 μg/litre in groundwater (the 85th percentile for all non-zero samples was 2 μg/litre in surface water and 0.12 μg/litre in ground water). Spalding & Snow (1989) detected propachlor at a maximum concentration of 46 μg/litre in stream water receiving its flow from agricultural land planted principally with corn. The monitoring was carried out during a spring period of high water flow and run-off.

5.1.3 Food

The residues of propachlor in potato tubers and tomatoes were lower than 0.005 mg/kg (the limit of detection) approximately 60-70 days after application of the recommended dose of 4-6 kg/ha (Balinova, 1981). Warholic et al. (1983) could not detect propachlor (detection limit, 0.06 mg/kg fresh weight) in cabbages grown on soil treated with propachlor at 0.6 kg a.i./ha (wettable powder).

Frank et al. (1977) reported the results of a study on the fate of propachlor applied to onions. Planted in May, the onions were

harvested in September and analysed in January the following year. Conjugated *N*-isopropylaniline was present in onion tissue after harvest and after a normal storage period for the crop before sale. Bearing in mind the reports of other authors (Lamoureux et al., 1971), Frank et al. (1977) suggested that 2-chloro-*N*-isopropylacetanilide could be hydrolysed to 2-hydroxy-*N*-isopropylacetanilide and bonded to glutathione. It is probable that alkaline hydrolysis cleaved the weaker N-carbonyl C linkage to given *N*-isopropylaniline rather than the stronger C-S bond which would have resulted in 2-hydroxy-*N*-isopropylaniline. Tissue residues of *N*-isopropylaniline increased as the rate of application of propachlor was increased, and the later the application was made the higher the tissue residues (see Table 7).

Table 7. Residues of conjugated *N*-isopropylaniline[a]

Year	Time of application	Rate of propachlor application (kg/ha)	*N*-isopropylaniline residues (mg/kg)
1974	untreated	0	0.03
	pre-emergence	7.2	0.05
		12.0	0.09
	pre-emergence and early post-emergence (21 May and 13 June, respectively)	7.2 + 7.2	0.17
		12.0 + 12.0	0.15
	pre-emergence and late post-emergence (21 May and 9 July, respectively)	7.2 + 7.2	0.28
		12.0 + 12	0.40

[a] From: Frank et al. (1977). Onions were planted 6 May 1974 and harvested 4 September 1974. Analyses were performed in January 1975.

Propachlor has been used for soil treatment (6 kg/ha) before planting tomatoes and peppers. Sampling was performed at 15-day intervals and the samples were analysed by gas chromatography (detection limits, 0.005 mg/kg). Small quantities of propachlor (of the order of 0.04 mg/kg) were found in tomatoes on the 70th and 85th days after soil treatment. On the 73rd day, 0.07 mg/kg was found in peppers, and on the 88th and 108th days the residues had decreased to 0.05 and 0.04 mg/kg, respectively. No herbicide residues were found in the following years (Balinova & Konstantinov, 1975).

In a study where soil was treated (8 kg/ha) before the seedlings were planted, samples of cabbages contained propachlor residues 0.6-0.8, 0.3-0.4 and 0.1-0.16 mg/kg after one, two and three months, respectively (Medved, 1977). No residues were detected in cabbages 96 days after the application of propachlor, at harvesting (Kolesnikov et al., 1979). A decrease in dose and application by conveyor belt perceptibly reduced the residues (Table 8).

Table 8. Residues (mg/kg) of propachlor in cabbages (type Amager 611)

Propachlor application rate	Date of application	Sampling time (no. of days after application)			
		13	33	64	96
8 kg/ha (before setting out)	31 May	0.6	0.3	0.1	No
8 kg/ha (after prior application of 5 kg/ha)	31 May	0.8	0.4	0.16	No
4 kg/ha (conveyor-belt application after setting out)	7 June	0.4	0.2	0.03	No

In a study by Nesterova et al. (1980), a dry soil area planted with cabbages was treated with propachlor (7 kg/ha) each year. In the second year no residues were detectable two months after application. In the third year, when the moisture content of the soil had increased, propachlor degradation was more rapid and no residues were detectable 15 days after the application. The soil was dry in the fourth year, and residues were detectable in cabbages up to two months after application.

Lottman & Cowell (1986) reported propachlor residues in sorghum grains of between < 0.02 and 0.24 mg/kg after treatment of soil at 4.4 kg/ha. Lottman & Cowell (1987) found residues in corn grain of < 0.02 to 0.04 mg/kg after soil treatment with propachlor at 4.4 kg/ha and of < 0.02 to 0.19 mg/kg after treatment at 6.6 kg/ha.

5.2 Occupational exposure

Only limited data are available on occupational exposure to propachlor. Its application by a tractor-mounted sprayer to cabbages resulted in its presence in the breathing zone of the tractor drivers at levels of 0.8 to 2.1 mg/m^3 (Panshina, 1977) and 0.1 to 3.7 mg/m^3 (Panshina, 1976).

6. KINETICS AND METABOLISM

6.1 Absorption

Propachlor may be absorbed through the respiratory and gastrointestinal tracts as well as through the skin. Following a single oral administration in mammals, it is rapidly taken up into the blood and internal organs, reaching its maximum blood concentration in 1 h. After 48 h it is no longer detectable in the organs (Panshina, 1985). An estimated 68% of a single 10 mg dose of ring-labelled ^{14}C-propachlor administered to 12 rats was recovered in urine 56 h later (Malik, 1986). These results are supported by those of other studies in which 54-64% (Lamoureux & Davison, 1975) and 68.8% (Bakke et al., 1980) of the administered dose was recovered in urine 24 h and 48 h after dose administration, respectively.

6.2 Metabolic transformation

Propachlor is rapidly metabolized. Its metabolism in animal species has been studied by Bakke & Price (1979), Pekas et al. (1979), Bakke et al. (1981a,b,c), Rafter et al. (1983a,b), Aschbacher & Struble (1987) and Davison et al. (1988, 1990). Most of the animal species studied metabolize propachlor through the mercapturic acid pathway (MAP). The intestinal microflora is involved in the metabolism of MAP intermediates (Bakke et al., 1981c). Metabolites of propachlor, in which chlorine from the parent compound (2-chloro-isopropylacetanilide) is removed by a nucleophilic displacement (Rafter et al., 1983a) by a cysteine group or methylsulfonyl group (CH_3SO_2), are present in the urine of rats dosed orally with propachlor (Larsen & Bakke, 1979). It has been shown that a cysteine conjugate of propachlor is the source of sulfur in methylsulfonyl-containing metabolites, but that the carbon in the methylsulfonyl group does not come from the cysteine moiety. Propachlor is conjugated firstly with glutathione and the reaction is mediated by glutathione transferases. The glutathione conjugation provides a means for inactivation of reactive electrophiles. Glutathione conjugates have the required physico-chemical properties for biliary excretion and will generally be present, together with their catabolites cysteinyl-glycine, cysteine and *N*-acetylcysteine-mercapturic acid, in relatively high concentrations in the bile (Rafter et al., 1983a). After excretion with the bile, they are metabolized in the intestine where the C-S lyase present cleaves the cysteine conjugate,

allowing further metabolism of sulfur to a methylsulfonyl-containing moiety (Larsen & Bakke, 1979).

The C-S lyase enzyme systems have been isolated in rat liver and bacteria demonstrating that they are of bacterial origin. As a good example, C-S lyase from *Fusobacterium necrophorum*, one of the pure intestinal bacteria, has been isolated and characterized as a key enzyme in mammalian metabolism (Larsen et al., 1983). This is confirmed by the fact that in germ-free rats (Bakke et al., 1980) (Fig. 2) and rats treated by antibiotics (Larsen & Bakke, 1981) ^{14}C was excreted from ^{14}C-propachlor as MAP metabolites, but there were no methylsulfonyl-containing metabolites in urine. Inextractable residues were eliminated in the faeces. This shows that MAP metabolites are available as substrates for the intestinal microflora. Of the MAP metabolites studied, the glutathione and cysteine conjugates are the best substrates both for production of 2-mercapto-*N*-isopropyl-acetanilide and for parallel formation of insoluble ^{14}C residues (Larsen & Bakke, 1983) which are excreted in the faeces.

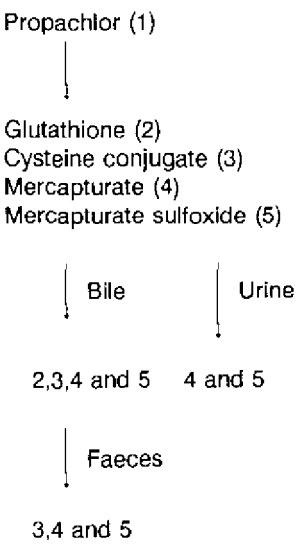


Fig. 2. Summary of the metabolism of propachlor in germ-free rats. From: Bakke et al. (1980).

In normal rats dosed with propachlor, the above-mentioned final metabolites were formed when MAP metabolites underwent a number of reactions: carbon-sulfur bond cleavage by microflora, S-methylation, S-oxidation, ring and alkyl-hydroxylation, glucuronide conjugation, N-dealkylation and amide cleavage (Rafter et al., 1983b).

Fig. 3 shows the proposed metabolic pathway for the formation of methylsulfonyl metabolites in rats and pigs (Aschbacher & Struble, 1987) and Fig. 4 the metabolism in normal rats treated with propachlor proposed by Bakke et al. (1980).

The tissue in which propachlor enters the mercapturic acid pathway has not been determined. The liver is an obvious site for glutathione conjugation, but the intestine cannot be excluded (Bakke et al., 1980). Organ perfusion studies have demonstrated that all enzymes necessary for the formation of mercapturic acid conjugates are present in the kidneys of both chickens and rats (Davison et al., 1988, 1990) and in the livers of rats (Davison et al., 1990). Rat caecal contents are similar to those of the pig with respect to C-S lyase activity, which explains the general similarity of their metabolic transformations (Larsen & Bakke, 1983).

When pig caecal contents were incubated with the glutathione conjugate of propachlor, the formation of both insoluble residues and the thiol increased with increase in incubation period (Table 9). Digestive peptidases extracted during isolation of the metabolites were thought to be the explanation for the presence of the cysteine conjugate in the zero time samples, because no cysteine conjugate was isolated from heat-treated caecal contents. A decrease in glutathione concentration with increased incubation time was also evident and was confirmation of a product-precursor relationship. This decrease in glutathione conjugate concentration was assumed to be caused by formation of cysteine conjugate (82%), due to cleavage by peptidase activity, in the caecum (Larsen & Bakke, 1983).

In summary, three or more enterohepatic cycles for propachlor metabolism in normal rats have been described. In the first, propachlor is metabolized via the mercapturic acid pathway and the conjugates are excreted in the bile. The second cycle is initiated when the biliary mercapturic acid pathway metabolites are metabolized by microbial/intestinal C-S lyase into reabsorbable metabolites (possibly 2-mercapto-*N*-isopropylacetanilide). The reabsorbable metabolites are further metabolized to

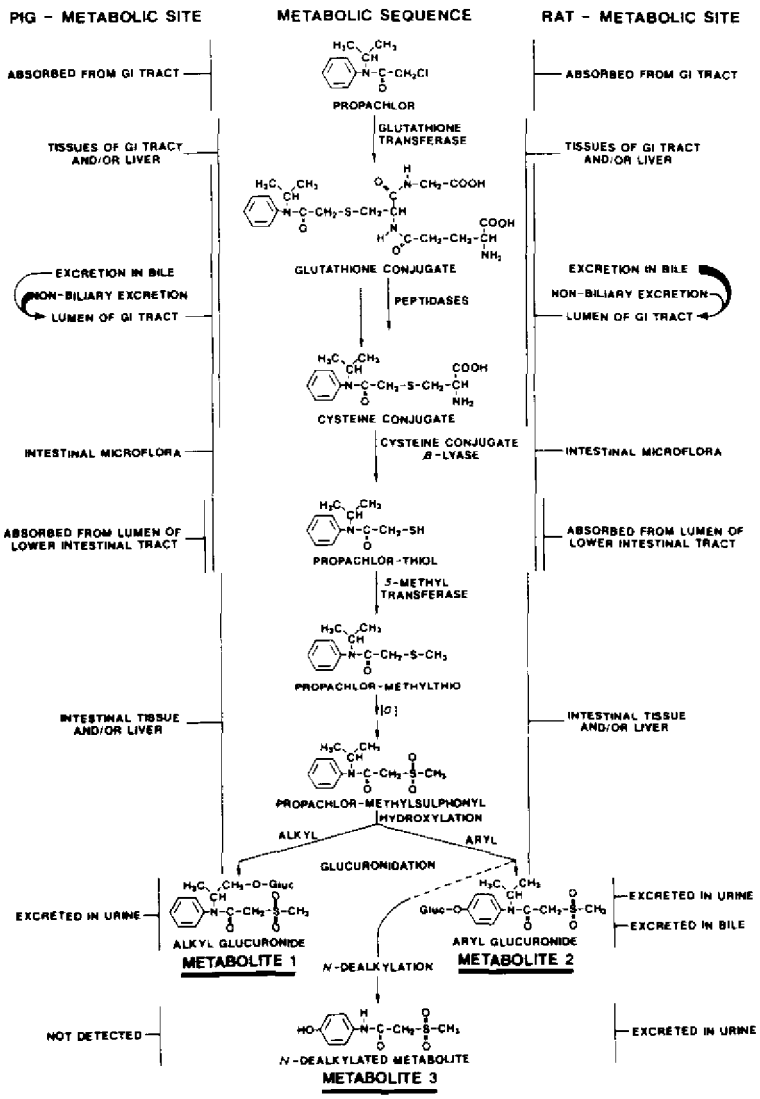


Fig. 3. Proposed metabolic sequence in the formation of methylsulfonyl metabolites by rats and swine.
From: Aschbacher & Struble (1987)

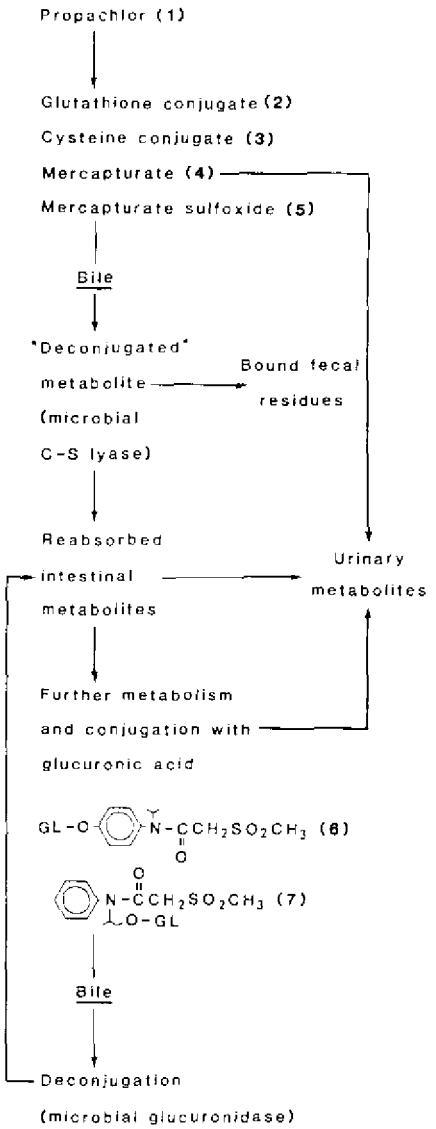


Fig. 4. A diagrammatic representation of the metabolism of propachlor in normal rats treated with propachlor.
Metabolites 6 and 7 are glucuronides.
From: Bakke et al. (1980)

Table 9. Incubation of the glutathione conjugate of propachlor with pig caecal contents for various durations[a]

Metabolites recovered	Incubation time					
	0	20 min	40 min	1 h	2 h	4 h
2-Mercapto-*N*-isopropyl-acetanilide	7.7[b] (5.1-10.6)	14.5[b] (5.5-22.8)	23.0[b] (15.8-36.0)	28.3[b] (22.9-38.7)	34.7[b] (21.8-44.0)	43.4[c] (38.7-49.2)
Glutathione conjugate of propachlor	26.8 (15.8-38.1)	36.0 (18.1-51.6)	20.8 (13.3-25.3)	28.8 (16.6-42.3)	21.5 (14.0-32.2)	16.5 (14.8-19.2)
Cysteine conjugate of propachlor	47.5 (36.0-51.5)	32.5 (21.3-43.7)	35.1 (30.5-41.9)	20.9 (12.0-27.9)	11.9 (10.9-12.5)	3.8 (2.2-5.6)
Non-extractable ^{14}C residues	13.1 (13.0-13.4)	12.9 (9.9-17.8)	16.0 (13.5-20.5)	16.6 (15.0-18.9)	25.4 (22.8-28.2)	33.9 (31.5-35.8)

[a] From: Larsen & Bakke (1983).
[b] Isolated as 2-carboxymethylthio-*N*-isopropylacetanilide
[c] Isolated as 2-(^{13}C)-carboxymethylthio-*N*-isopropylacetanilide
Pigs were gilts. Results are shown as a percentage of the substrate. Values given in parentheses represent the range of values obtained from ^{14}C-recovery measurements.

glucuronides by glucuronidase enzymes, and these are secreted with the bile. These biliary glucuronides subsequently initiate the third cycle in the enterohepatic circulation of propachlor metabolites.

No doubt the intestinal microorganisms complicate the metabolism of propachlor (in comparison with the situation in germ-free and antibiotic-treated rats) and create new non-polar compounds from the products of the mercapturic acid pathway, which are reabsorbed into the blood. These new compounds have to be converted again into polar products in order to be excreted (Bakke et al., 1980).

More recent studies carried out by Aschbacher & Struble (1987) on the metabolism of propachlor in pigs have proved the similarity, i.e. the formation of methylsulfonyl-containing metabolites, with the metabolism of rats, but have also revealed some differences.

A pig with a cannulated bile duct, which was dosed orally with ^{14}C-propachlor, excreted 7.6% of the dose in the bile compared with approximately 75% in the case of the rats. When enterohepatic circulation was prevented in the bile of cannulated pigs, CH_3SO_2-containing metabolites of propachlor were excreted in the urine. As mentioned above, enterohepatic circulation is necessary for the production of methylsulfonyl-containing metabolites in rats. In experiments with germ-free pigs dosed orally with ^{14}C-propachlor, it was shown that they did not excrete urinary CH_3SO_2 metabolites, which indicated involvement of the intestinal flora in the production of these metabolites, as occurs in rats. Non-biliary excretion of metabolites of propachlor into the lumen of the intestine probably occurred. It is presumed that propachlor is absorbed by the mucosal cells and conjugated with glutathione and that some of this conjugate moves directly into the lumen of the intestinal tract by simple diffusion, where it becomes the substrate of bacterial beta-lyase. The presence of glutathione transferase has been demonstrated previously in subcellular fractions of mucosal tissue homogenates.

In situ intestinal absorption of propachlor and non-biliary excretion of metabolites into the intestinal tract of rats, pigs and chickens was studied by Struble (1991). Propachlor was absorbed from *in situ* intestinal loops of rats and pigs, the absorption half-times being 7.5 and 16.5 min, respectively. Water-soluble ^{14}C-labelled metabolites that accumulated in the intestinal loops

accounted for 31%, 53% and 25% of the initial ^{14}C in rats, pigs and chickens, respectively. Propachlor-S-cysteine was identified as the major metabolite in the pig intestinal lumen (43% of the water-soluble ^{14}C). It was concluded that the intestinal metabolism and intestinal excretion of water-soluble metabolites of propachlor are important physiological processes that occur in a variety of animal species. These processes provide a route by which metabolites of xenobiotics may reach the intestinal lumen in animals that are poor biliary excretors. These studies demonstrated that although bile may be the major route by which MAP metabolites are made available to the intestinal microflora in the rat, an extrahepatic route exists in the pig.

Davison (1991) conducted a study using six anaesthetized 2- to 21-day-old male Guernsey calves weighing 28 to 61 kg in which either the left kidney was perfused (via the left renal artery) or the left ureter was perfused with metabolites of propachlor. The glutathione conjugate of propachlor (2-*S*-glutathionyl-*N*-acetylacetanilide) was metabolized in both kidney and ureter to the cysteine conjugate. When the mercapturic acid conjugate of propachlor was presented to the kidney, it was eliminated in urine. First-pass metabolism and elimination of the glutathione conjugate by the kidney was 16% of the dose, whereas first-pass elimination of the mercapturic acid was 33%. Absorption of the glutathione conjugate of propachlor or its metabolites, or of glycine by the ureter was nil. The cattle may be unable to form mercapturic acids from glutathione conjugates of some xenobiotics, which may result in their being more easily poisoned by these xenobiotics than chickens, pigs and rats.

The glutathione conjugate of 2-chloro-*N*-isopropyl[1-^{14}C]acetanilide (^{14}C-propachlor) was perfused through a calf kidney *in situ* by Bakke et al. (1990). Twenty-three per cent of the dose was excreted in the perfused kidney urine as the cysteine conjugate; no mercapturic acid was detected. A 5-day-old calf dosed orally with ^{14}C-propachlor excreted 70% of the dose in the urine as the cysteine conjugate; again no mercapturic acid was detected. Rumen microflora were established in the calf when it was 5 weeks older and the experiment was repeated. The same results were obtained.

6.3 Elimination and excretion

When ^{14}C-propachlor was given to rats, 56-64% of the dose was excreted in urine in the first 24 h and 5.7-7.0% in 24-48 h. In the

faeces, 8-13% and 2.2-7.7% were eliminated in 0-24 h and 24-48 h, respectively; 0.4% of the ^{14}C was eliminated as CO_2 and 5-11% was in the carcass. In total 80-97% was eliminated in 48 h (Lamoureux & Davison, 1975).

According to Bakke et al. (1980), the metabolites of propachlor formed in normal rats treated with propachlor are excreted mainly through urine (68%) and faeces (19%). Eleven urinary metabolites were isolated from rats given ^{14}C-labelled propachlor orally. The major metabolite was the mercapturate (17%), and six of the metabolites were 2-methylsulfonylacetanilides. Faecal residues (19%) of the administered dose, insoluble in common solvents or by treatment with diluted acid or base, were also determined.

Rats with cannulated bile ducts secreted 66% of an oral dose of propachlor in the bile as the glutathione conjugate (2), cysteine conjugate (3), mercapturate (4) and the mercapturate sulfoxide (5) (see Table 10). Germ-free rats given orally ^{14}C-labelled propachlor excreted 98% of the dose in the urine and faeces within 48 h. Three metabolites were isolated from the excreta and the faecal radioactive metabolites were water soluble. The major metabolite was mercapturate (4) and the other metabolites were the cysteine conjugate (3) (present only in the faeces) and mercapturate sulfoxide (5) (Bakke et al., 1980). Mercapturate sulfoxide was isolated from the excreta of germ-free rats by Feil et al. (1981), who also demonstrated its presence in the bile of rats and urine of chickens and pigs dosed with propachlor. The metabolite was characterized by mass and nuclear magnetic resonance spectrometry on samples isolated from rats.

As in the case of the glutathione and cysteine conjugates, the sulfoxide is not excreted at detectable levels by normal rats and was detected only in the bile (Bakke et al., 1981a). It may become a substrate for the intestinal flora, but the ultimate *in vivo* fate of this metabolite is unknown.

Bakke et al. (1981c) reported differences between some species concerning the metabolism of propachlor in the MAP. Clear but unexplained differences are that rats excrete no cysteine conjugate and chickens form no methylsulfonyl-containing metabolites, whereas sheep excrete large amounts of cysteine conjugate in urine.

Nadeau & Pantano (1986) carried out a study to determine the rates and routes of excretion of orally administered synthetic

Table 10. Comparison of the excretion of single oral doses of ^{14}C-propachlor by control rats with fistulated bile ducts, and germ-free rats[a]

Metabolite	Recovery of ^{14}C (% dose)[b]				
	Control rats		Bile-fistulated rats	Germ-free rats	
	Urine	Faeces	Bile	Urine	Faeces
Glutathione conjugate (2)[b]			37		
Cysteine conjugate (3)			13		19
Mercapturate (4)	17		12	63.1	3.7
Mercapturate sulfoxide (5)			4	5.7	5.4
Non-extractable residues		19			
Other metabolites	51				
Total	68	19	66	68.8	32.1

[a] From: Bakke et al. (1980)
[b] Metabolite designations are those used in Figs. 1 and 3.

^{14}C-labelled propachlor plant metabolites in lactating goats and to quantify and identify the radioactive metabolites in the goat milk, tissues, urine and faeces. The daily dose level for the three treated goats was 15 mg/kg administered on 5 consecutive days (the actual dose levels for the treated goats were 13, 14.5 and 13 mg/kg, respectively). Each treated goat received a total of 130.5 mg of the ^{13}C/^{14}C-labelled propachlor plant metabolites mixture during the dosing period. A control animal received placebo capsules. The radioactivity eliminated in faeces accounted for 72.1, 64.5 and 57.9% of the administered dose, respectively (average 64.8%), and that excreted in urine accounted for 35.8, 28.1 and 32.3% (average 32.1%). The percentage of the dose eliminated through faeces and urine averaged 96.9%.

The radioactivity found in the milk accounted for only 0.084, 0.10 and 0.13% (average 0.10%) of the administered dose. These values corresponded to metabolite concentrations in the milk of 11.9, 14.8 and 18.0 μg/litre (average 14.9 μg/litre). The metabolic concentrations (μg/kg) in the tissues were: kidney 51.9, liver 30.4, muscle 8.5, fat 19.5 and blood 50.1. The loss of radioactivity from tissues, milk and excrement occurred rapidly, and after 5 days of depuration the milk and tissue radioactivity levels were below the limit of detection, except in the case of the liver (5.7 μg/kg).

6.4 Metabolism in laying hens

Since crops treated with propachlor are used in animal feed, it is important to know the fate of propachlor in animal feed.

The purpose of the study by Bleeke et al. (1987) was to examine the metabolic fate of propachlor plant metabolites in laying hens and to determine whether they accumulate or persist in the eggs or edible tissues. The compounds used for feeding were the three major metabolites of propachlor found in sorghum, i.e. [(*N*-isopropyl)-phenylamino] oxacetic acid, sodium salt (I), {{[(*N*-isopropyl)-phenylamino]acetyl}sulfinyl} lactic acid, sodium salt (II) and 2-[(*N*-isopropyl)-phenylamino] 2-oxoethane sulfonic acid, sodium salt (III).

The first study involved dosing chickens at a level of 5 mg/kg diet for 6 consecutive days. Data for bioaccumulation and excretion of plant metabolites were obtained from this study. A second group of chickens, dosed at a level of 25 mg/kg diet (nominal dose) on 6 consecutive days, provided eggs and tissues with higher residues for metabolic characterization. Each group consists of five hens. Control groups received a single gelatine capsule per day. The total recovery of ^{14}C radioactivity was good in both studies.

An average of 87.4% of the total administered dose was recovered from the chickens fed 5 mg/kg approximately 1 day after the last dose, and 97.9% was recovered from the chickens fed 25 mg/kg, primarily in the excreta. The eggs contained low residue levels; those from chickens fed 5 mg/kg contained residues below the minimum quantifiable limit (MQL) of 1.7 μg/kg. The level in the egg yolks reached an average of 5.5 μg/kg by day 6 but by day 12 the residues in the yolk had fallen below 1.6 μg/kg.

In the high-dose group, the residues in the egg white levelled off at about 4 μg/kg on day 2, while those in the egg yolk increased to a level of 27.3 μg/kg on day 6.

Tissues also contained low levels of residues. In the low-dose group, the highest levels were found in the kidney and they averaged only 6 μg/kg. The residue levels in the liver measured an average of 1.9 μg/kg and those in the fat 3.5 μg/kg. The residues in other fat samples and organs were below the MQL (1.4-1.6 μg/kg). Residues in the breast muscle were below the minimum detectable limit (7 μg/kg) and those in the blood were 6-7 μg/kg.

7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

7.1 Single exposure

7.1.1 Oral

The acute oral toxicity of propachlor for the rat, mouse and the rabbit has been examined. According to the WHO hazard classification of pesticides and as far as its acute oral toxicity to rats is concerned, propachlor is slightly hazardous (Group III) (WHO, 1990). LD_{50} values in various animal species reveal a higher susceptibility for the mouse and the rabbit than for the rat (Table 11). The LD_{50} for rats ranges from 950 to 2176 mg/kg.

The clinical picture of acute oral intoxication by propachlor has been described in three species of experimental animals: mice, rabbits and rats (Panshina, 1973). When propachlor is given at lethal or toxic doses, the main symptoms concern the central nervous system. In mice and rabbits, a state of excitement, trembling and light convulsions is observed 15 min after a toxic or lethal dose of propachlor. This gradually increases, breathing becomes difficult and death follows in several hours. Intoxication in rats takes a different course: a state of immobility and head and body tremors are accompanied by the sudden onset of convulsions and death occurs within 24 h. This clinical picture was confirmed by Strateva (1974,a,b).

Kronenberg (1988) reported clear signs of irritation to the gastrointestinal tract and lungs that were evident at necropsy in animals that died during the study. Histoenzymological changes expressed as decreased enzyme activity were in full agreement with the morphological picture (Strateva et al., 1974a,b).

7.1.2 Dermal

Results of studies in rabbits on the acute dermal toxicity of propachlor and its formulations indicate that the dermal LD_{50} ranges from 4000 mg/kg for a 65% WP formulation (Auletta & Rinehart, 1979) to 20 000 mg/kg for technical propachlor (94.5%) (Braun & Rinehart, 1978). Test animals exhibited moderate to severe erythema, severe oedema and necrotic skin at the dermal application sites at a dose level of 2800 mg/kg. Motor activity decrease and ataxia were noted at dose levels of 2000 to 5600 mg/kg.

Table 11. Oral LD_{50} values for laboratory mammals

Species	LD_{50} (mg/kg)[a]	Reference
Rat	1056 (834-1278)	Panshina (1973, 1977)
	950 (860-1050)	Strateva (1974b)
	1340	Mirkova (1975)
	2176 ± 220	Lehotzky et al. (1979)
Rat (Sprague-Dawley)	840 (419-1261) (in corn oil)	Błaszcak (1988)
	1700 (1265-2135) (in 1% methylcellulose)	Blaszcak (1988)
Rat (Fischer-344)	550 (252-848) in corn oil	Blaszcak (1988)
	1359 (1009-1691) (in 1% methylcellulose)	Blaszcak (1988)
Rat (both sexes)	4000	Heenehan et al. (1979)
Rat (both sexes)	3269	Branch et al. (1982a)
Mouse	306 (275-337)	Panshina (1973, 1977)
	290 (240-350)	Strateva (1974b)

[a] The concentration is based on the percentage active ingredient. Figures in parentheses indicate the range of values.

Using groups of 16 Wistar rats, Baynova et al. (1977) studied the acute dermal toxicity of a single application of propachlor 65 WP (10-20% in aqueous suspension) with doses of 1500-4000 mg/kg body weight (active ingredient). There was no mortality, and no signs of intoxication were observed. No haematological or biochemical tests were performed.

Propachlor and Satecid 65 WP caused severe dermatitis, ulceration and necrosis in the skin of rabbit and ears of mice. None of the compounds exhibited contact sensitization effects on guinea-pigs (Lehotzky et al., 1979).

7.1.3 Inhalation

In a study by Bechtel (1991), technical propachlor (96.8%) was dissolved in dimethylsulfoxide (DMSO) to generate an aerosol and administered to five male and five female Sprague-Dawley rats in a nose-only chamber at an analytically determined concentration of 1.2 mg/litre for 4 h. Control rats (five of each sex) were exposed to an atmosphere of aerosolized DMSO for the same duration. Particle size measurements on the propachlor/DMSO aerosol indicated a mass median aerodynamic diameter of 3.5 μm, with 96% of the particles being less than 10 μm and 1.8% less than 1 μm in diameter (Bechtel, 1991). No treatment-related deaths occurred. Clinical signs included laboured respiration and nasal discharge; all animals appeared normal by post-exposure day 2. A transient weight loss was noted in both treated and control animals during the first two days of the study, but normal body weight was observed thereafter. No abnormalities were apparent during postmortem examination of the animals.

In another acute inhalation study, three groups of Charles River CD rats (five rats of each sex per group) were exposed to test atmospheres of a propachlor formulation (44% active ingredient) for 4 h (Kaempfe, 1991). During the exposure period, animals were housed in a 250-litre New York University style stainless steel chamber, and were exposed to analytically confirmed concentrations of 0.18, 0.67 and 1.0 mg propachlor/litre in the breathing zone of the chamber. At least 82% of the particles were less than 10 μm in diameter. No animals died at the two lower exposure levels, whereas four out of ten rats died at 1.0 mg/litre. Clinical observations during the post-exposure period included ocular opacities, perinasal encrustation, rapid or shallow respiration, perioral wetness and focal loss of hair from animals in the highest exposure group. Fourteen days after exposure, all surviving animals had body weights higher than the pre-exposure (day 0) values with the exception of females in the 1.0-mg/litre group, which exhibited body weight depression. There were no abnormal findings in rats that died during the test or were sacrificed at 14 days. Based on the mortality observed, the LC_{50} was slightly greater than 1.0 mg/litre.

7.2 Short-term exposure

7.2.1 Oral

7.2.1.1 Dogs

To assess potential subchronic toxicity, propachlor (96.1% pure) was administered via the diet to five groups of two male and two female beagle dogs for 4 weeks (Daly & Knezevich, 1984). Dietary concentrations of propachlor were 0, 100, 500, 1000 and 1500 mg/kg (equivalent to 0, 2.5, 12.5, 25, and 37.5 mg/kg body weight per day). No mortality or clinical signs of toxicity related to treatment occurred during this study. Food consumption was initially decreased, but only in the females treated with 1000 and 1500 mg/kg (equal to 25 and 37.5 mg/kg body weight) and the males treated with 1000 mg/kg. The consumption had returned to normal by the end of the study. Body weight varied markedly. The decreased body weight and/or weight gain noted in males fed 12.5 or 25 mg/kg body weight per day, and females fed 37.5 mg/kg per day could have been treatment related. Haematological examination showed slightly increased platelet counts in high-dose males. No treatment-related gross pathological effects were noted at sacrifice.

Following the 4-week pilot feeding study in beagle dogs, a 90-day feeding study was undertaken (Naylor & Ruecker, 1986). Propachlor (96.1% purity) was administered in the diet to groups of six dogs of each sex per group for 90 days. Nominal dietary concentrations were 0, 100, 500 and 1500 mg/kg. There was no mortality or clinicopathological or histopathological changes related to the treatment. The dose level of 1500 mg/kg (45 mg/kg body weight) was a no-observed-adverse-effect level (NOAEL).

7.2.1.2 Rodents

Propachlor (65% WP) was given orally by gavage to white rats at daily doses of 21, 53 and 106 mg/kg body weight for 4 months, and its cumulative effect was studied by Panshina (1973). Later, Strateva (1974a, 1976) carried out a short-term study (45 days) at dose levels of 50, 100 and 200 mg/kg body weight given orally by gavage to 104 Wistar rats (divided into four groups (three experimental and one control) with equal numbers of both sexes), and a long-term oral study (6 months) at dose levels of 0.05, 0.5, 5 and 20 mg/kg body weight given to 220 Wistar rats divided into five groups (four experimental and one control).

Strateva (1976) found a decrease in haemoglobin content and number of erythrocytes, slight leucocytosis and an increased number of neutrophils. The threshold dose for rats in long-term studies was 5 mg/kg body weight.

Panshina (1976) carried out a 10-month study on white rats given propachlor by gavage at doses of 1, 3.5 and 10.6 mg/kg body weight. Slight leucocytosis was found within 4-7 months. The first two doses provoked a decreased activity of catalase and peroxidase as well as an increase in nicotinamide adenine dinucleotide in brain and heart tissue homogenates. No changes in haemoglobin content or number of erythrocytes were noted. There were no alterations to the pathomorphological picture.

Baynova et al. (1978a) compared the effects of continuous and intermittent oral dosing of propachlor (65% WP) on white rats (equal numbers of both sexes). The number of animals per group was not given. The scheme of the experimental design is given in Table 12.

Table 12. Experimental design of the study by Baynova et al. (1978a)

Group	Duration of study	Daily dose (mg/kg)	Dose (fraction of the LD_{50})
Control	4 months	-	-
I (dosing every week)	4 months	70	1/20
II (dosing every second week)	4 months	140	1/10
III (dosing every second week)	8 months	70	1/20
Control	8 months	-	-

Continuous administration of propachlor led to more marked changes in the main parenchymous organs than intermittent administration. These changes were characterized by decreased activity of oxido-reductive tissue enzymes. The hexabarbital sleeping time, which characterized the detoxification function of the liver, showed a statistically significant reduction. Propachlor administration at 120 mg/kg body weight for 6 consecutive days

to male and female rats increased the levels of both cytochrome and microsomal protein content (Nenov & Baynova, 1978) as a result of the induction of mixed-function oxidase in the liver (Baynova et al., 1978a).

A special study on the morphological changes in kidneys was carried out. Propachlor (65% WP) was administered by gavage to male white rats (10 animals per group and 1 control) at doses equivalent to 6, 12 and 60 mg/kg body weight for 3 months (Maleva & Zlateva, 1982). Dose-dependent morphological changes were found in the proximal convoluted renal tubules. The tubules were deformed and the epithelial cells were vacuolized and dystrophic. A decreased cellular content of ribonucleoproteins was also observed and pycnosis and caryolysis of nuclei were seen. In the lumen, desquamated epithelia and hyalin cylinders were found. The intestine was slightly swollen in certain areas.

The subchronic toxicity of propachlor (96.1% purity) has also been evaluated in Sprague-Dawley CD rats (30 of each sex per group) fed diets containing 0, 300, 1500 or 7500 mg/kg for 90 days (Reyna & Ribelin, 1984a). No animals died. A statistically significant reduction in body weight was observed in animals fed 1500 mg/kg (8% for males and females) and 7500 mg/kg (59% for males and 36% for females). Food consumption was significantly depressed for animals at the highest dose level for the first month of the study, but recovered during the remainder of the study. After 6 weeks, reduced haemoglobin, haematocrit, mean corpuscular haemoglobin and haematocrit, and an increase in reticulocytes were observed in females at all dose levels and in high-dose males. The anaemia was less evident in high-dose males and was only present in high-dose females at study termination. Significantly reduced lymphocyte counts were observed at week 6 for high-dose males and mid- and high-dose females, and at study termination for all groups. Levels of serum enzymes (SGPT, SAP, GGT), cholesterol and total bilirubin were significantly increased for high-dose animals at weeks 6 and 13 and there were significant reductions in total protein, glucose, creatinine and albumin. No histological changes were observed in the liver. Organ weights (with the exception of female livers) were reduced, relative to controls, for high-dose animals, and spleens were extremely small and treatment-related in size in about 65% of the animals. No histological changes were observed in the tissues examined, which included the spleen.

7.2.1.3 Mice

The subchronic toxicity of propachlor (96.1% pure) was evaluated in four groups of Charles River CD-1® mice (30 mice of each sex per group) (Reyna & Ribelin, 1984b). Dietary levels were 0, 500, 1500 and 5000 mg/kg. No mortality or adverse clinical signs were observed during the study. A statistically significant reduction (10%) in body weight was observed in the mid- and high-dose males and females during the study. Food consumption was also reduced during the first month for mid- and high-dose animals. A dose-related statistically significant reduction in the number of white blood cells was observed in both sexes at all dose levels, except low-dose females, at the 7-week sampling period. At study termination, this reduction was evident in mid- and high-dose animals but was statistically significant only for high-dose males. Liver weights were increased for males at all dietary levels and for mid- and high-dose females. There was an accompanying statistically significant increase in the incidence of centrilobular hepatocellular hypertrophy for mid- and high-dose males, based on histological examination. No other microscopic changes that could be considered treatment related were evident in tissues. For males, the kidney to body weight ratio was decreased at the high-dose level.

7.2.2 Dermal

A 21- and 90-day short- and longer-term dermal toxicity study on Wistar rats (12 animals in each tested group plus 1 control) using propachlor (65% wettable powder) administered 5 days per week was carried out by Baynova et al. (1977). The doses applied were 50, 200 and 500 mg/kg in aqueous suspensions in the 21-day experiment, and 10, 25 and 50 mg/kg in the 90-day study. The dermal application was performed uncovered (Draize, modification of Noakes). By the end of day 21, anaemia was found at dose levels of 200 and 500 mg/kg, but there was no methaemoglobinaemia. The same doses induced a statistically significant decrease in the activity of certain enzymes (SGOT, SGPT, OCT and AP). Dermal application of propachlor at dose levels of 25 and 50 mg/kg to the skin of white rats (two groups of 12 animals) for 90 days did not provoke any changes in concentrations of red blood cells and haemoglobin, but there were decreases in SGOT, SGPT, LAP, AP and catalase. Decreased sulfur-containing enzymes were found in tissue homogenates (liver and kidney). Decreases in the levels of LDH, SDH, AcP and glucose-6-phosphate dehydrogenase were determined

histochemically. There was no evidence of clinical signs of intoxication after repeated dermal application of the herbicide, but the occurrence of the above-mentioned enzymatic changes demonstrated the penetration of this herbicide through the dermal barrier. The hexabarbital sleeping time was statistically significantly shortened at the mid- and high-dose levels, thereby confirming the induction of mixed-function oxidases reported by Nenov & Baynova (1978).

A threshold dermal dose of 25 mg/kg (1% aqueous suspension of propachlor 65 WP) and a no-observed-effect level (dermal) of 10 mg/kg (0.5% aqueous suspension) were determined in 90-day experiments by Baynova et al. (1977).

7.3 Skin and eye irritation; sensitization

7.3.1 Skin irritation

Single application to Wistar rats (three rats of each sex per group) of propachlor 65 WP at doses of 1500, 2000, 3000 and 4000 mg/kg in 10 or 20% aqueous suspension, under the open modified method of Noakes, did not cause any local irritative effects (Baynova et al., 1977).

Panshina (1973) reported a strong irritative effect of propachlor after single and repeated application. Single applications to rabbits of 16% propachlor 65 WP in aqueous suspension at doses of 500, 700, and 1000 mg/kg led to hyperaemia and even ulceration in the skin of some animals. Ten applications of a 32% aqueous suspension of propachlor at a level of 200 mg/kg had the same effect on the skin. Seventeen applications of a 6.5% aqueous suspension at 100 mg/kg did not result in mortality, and only slight hyperaemia was seen in the treated skin area of the rabbits.

Primary irritation and contact sensitization effects of Satecid 65 WP containing 65% propachlor were investigated in rabbits, mice and rats, and these were compared with the effects of technical grade propachlor, propachlor with analytical purity, and the vehicle alone (Lehotzky et al., 1979). Propachlor had strong to very strong irritating effects on intact and scarified skin as well as on the eye mucosa of rabbits and mice. The symptoms included erythema, oedema and penetrating ulcer. Technical grade propachlor had the most potent irritating effect.

Heise et al. (1983) conducted parallel experiments with two propachlor preparations, one produced in the USA and the other in Hungary, using an aqueous suspension applied under occlusion to the skin of rabbits for 24 h. The irritant dose (ID_{50}) for the USA preparation was 2% and for the Hungarian preparation 0.6%.

Several dermal irritation studies have been carried out with technical propachlor and its formulations, each of which involved the use of six New Zealand white rabbits (2.5 to 3.5 kg). All application sites were scored for erythema, eschar and oedema formation. For technical propachlor (94.5% pure) a slight degree of dermal irritation was observed (2.5/8.0 score) (Braun et al., 1979a); for a 20% formulation of propachlor (again 94.5% pure) there was a slight degree of dermal irritation (1.8/8.0 score) (Braun et al., 1979b); for a 65% formulation a moderate degree of dermal irritation (3.4/8.0 score) (Braun et al., 1979c); and for a 42% formulation corrosive effects were observed (Branch et al., 1982b).

7.3.2 Skin sensitization

A modification of the maximalization test of Magnusson & Kligman (1969) for identification of allergens was used by Heise et al. (1983). Guinea-pigs (12 female and 12 male) were treated by intramuscular injection of 0.2% propachlor aqueous suspension (using preparations from both the USA and Hungary together with Freund adjuvant), by subcutaneous injection of 0.05% aqueous suspension and by epicutaneous application of a 1% water suspension of both preparations for 6 weeks, both on healthy and scarified skin. A challenge single application was given two weeks after the last application using 0.2 ml of an 1% aqueous suspension of each formulation. There was no significant difference between the reactions to the two preparations. A challenge dose did not induce a reaction.

The dermal sensitization potential of propachlor was evaluated in guinea-pigs using the Buehler procedure (Auletta, 1983). For the induction phase, 0.2 ml of undiluted propachlor (95.7% purity) was applied dermally using the closed patch technique to the shaved backs of five male and five female Hartley albino guinea-pigs. The applications were made for 6 h/day, 3 days/week, for 3 weeks. Two weeks after the final dose, additional 0.2 ml doses of 25% propachlor in ethanol (challenge dose) were applied to previously untreated areas on those guinea-pigs that had received the induction doses and to six others (three males and three females) which served as irritation controls. Two positive control

groups, treated with 1-chloro-2,4-dinitrobenzene (DNCB) as positive control, were used. The negative control group (five males and five females) was treated with saline for the induction doses and challenged with acetone. All animals had slight to moderate dermal irritation following the third induction dose of propachlor, and some of them exhibited severe irritation, including oedema, necrosis and exfoliation. Following application of the challenge dose, one out of ten animals had an irritation score of 1 (slight), eight animals had a score of 2 (moderate) and one animal had a score of 3 (severe) at 24 h. Nine of these animals exhibited oedema. At 78 h, two animals had very low scores, six animals had scores of 1, and two scores of 2. Six of these animals exhibited oedema. Similar results were obtained when 20 and 40% propachlor formulations were tested for sensitization in guinea-pigs (Auletta et al., 1984a,b).

7.3.3 Eye irritation

Molnar & Paksy (1978) studied the effect of Satecid 65 WP on the eye mucosa of CFY male albino rats using the Evans blue diffusion technique. The aqueous suspension caused strong conjunctivitis at the minimum concentration of 0.01%.

In a study by Auletta (1984), technical propachlor (96.1% pure) was ground to a fine powder and introduced in the conjunctival sac of the right eye of six (two males and four females) albino New Zealand White rabbits. The left eye served as the control. The treated eyes were rinsed 24 h later. Five of the animals exhibited severe conjunctival irritation (redness, necrosis, chemosis and discharge), five exhibited opacity and/or ulceration, and five had iridial damage. Two animals exhibited neovascularization of the cornea and one bulging of the cornea, indicative of increased intraocular pressure. After 21 days of observation one animal continued to exhibit conjunctival redness and one corneal opacity and bulging of the cornea. The eyes of the remaining animals had minimal conjunctival irritation.

In an eye irritation test on six New Zealand white rabbits using technical propachlor (94.5%), 0.1 cm^3 was instilled into one eye of each rabbit and ocular reactions were observed on days 1, 2, 3, 4, 7, 10 and 14. According to Draize scores, all treated eyes were assigned positive scores for corneal opacity and ulceration, conjunctival redness, chemosis and necrosis. Two eyes were assigned positive scores for iritis. Three eyes exhibited pannus, and corneal bulge was observed in two eyes. Four eyes were clear

of signs of irritation by day 14 and two eyes showed signs of irritation at the termination of the study (Braun, 1979).

US EPA (1984b) reviewed the existing data and concluded that propachlor is corrosive to the rabbit eye, corneal opacity being irreversible after 7 days.

7.4 Reproduction, embryotoxicity and teratogenicity

7.4.1 Reproduction

7.4.1.1 Biochemical and histopathological studies on gonads

The effect of propachlor 65 WP on protein content, activity of 5-nucleotidase and ATP in testis homogenate was evaluated by Maleva & Stereva (1977), Stereva & Maleva (1977) and Zlateva & Maleva (1978, 1979). Each test group consisted of 20 male Wistar rats, administered orally (by gavage) 12 or 60 mg propachlor/kg body weight per day for 6 months. A control group consisted of the same number of animals. At the end of the experiment, there were dose-dependent statistically significant changes in the biochemical indices studied (a decrease in protein content and an increase in 5-nucleotidase and ATPase activity) and these were accompanied by histomorphological changes, i.e. disorganization of the seminiferous epithelium. After prolonged dosing some dystrophic and degenerative changes in the gonad tissue and the appearance of multinuclear giant cells with central chromatolysis were observed. Adverse effects on the mitotic division of spermatogonia and blockage of meiosis in the earlier phases were found (Zlateva & Maleva, 1978, 1979).

In subchronic toxicity studies, there was no microscopic evidence of testicular pathology in dogs administered the equivalent of 45 mg propachlor/kg diet per day (Naylor & Ruecker, 1986), in rats fed the equivalent dose of 250-310 mg/kg diet per day in the food (Reyna & Ribelin, 1984a), or in mice fed the equivalent of 400 to 600 mg/kg diet per day (Reyna & Ribelin, 1984b).

7.4.1.2 Reproduction studies

A two-generation rat reproduction study was undertaken to evaluate the effects of propachlor (96.3% pure) (Rao, 1981). Four groups of 30 male and 30 female 6-week-old Fischer-344 rats (F_0 generation) were exposed to diets adjusted weekly to provide dose

levels of 0, 0.3, 3 and 30 mg propachlor/kg body weight per day for 100 days and were then allowed to mate to produce the F_1 generation. The F_1 weanlings were similarly dosed for 120 days prior to breeding. The F_1 adults were mated twice to produce F_{2a} and F_{2b} litters. At weaning of F_1, F_{2a} and F_{2b} litters, 10 pups of each sex at each dose level were sacrificed and selected organs were examined histologically. No signs of toxicity in any animals were found during the study. A significant decrease in food consumption and body weight of adult F_1 males dosed with 30 mg/kg per day was found. No adverse effects in any of the treated groups over two generations were noted with respect to gestation length, number of live pups delivered, neonatal survival, litter weight and sex ratio. Decreased pregnancy rates (fertility index) were observed in mid-dose (60%) and high-dose (63%) F_1 females following the first mating (F_{2a} litter), in comparison with 83% in the control rats. Test animals continued to be treated with propachlor and were remated to produce a second (F_{2b}) litter. Pregnancy rates for the F_{2b} litter were 83% for controls and 83, 83 and 80% for low-, mid- and high-dose groups, respectively.

No treatment-related gross necropsy findings were noted. Slight increases in absolute and/or relative liver weights were noted in high-dose F_0 adults, mid- and high-dose F_1 adults and high-dose F_{2a} weanlings. Hypertrophy of the centrolobular hepatocytes was noted during microscopic examination of livers from the high-dose F_0 and F_1 adult females. There was no evidence of compound-related microscopic changes in the testes and ovaries of test animals for either generation.

7.4.2 Embryotoxicity and teratogenicity

7.4.2.1 Rats

a) Single dose treatment

Mirkova (1975) reported embryotoxic and teratogenic effects of propachlor 65 WP in Wistar rats following single-dose treatment (675 mg/kg body weight) on each of the first 16 days of gestation. Significantly increased lethality and frequency of haematomas, predominantly in the head of the fetuses, and reduced cranio-caudal size were observed when the treatment was performed from days 1 to 4 and on days 8, 10 and 12 of gestation (8 to 12 animals per test group and 57 controls). The effect was more marked following treatment on the first day of pregnancy. A weak teratogenic effect was observed with a single dose, which included

the induction of external malformations (day 11, brachygnatia), abnormality of internal organs, i.e. hydrocephalus (days 9, 11, 12 and 13 of gestation), defects in skeletal ossification, i.e. non-ossification of sternum (day 9), and delayed ossification of parietal bones (days 11, 12 and 13 of gestation).

b) Repeated dose treatment

Wistar rats were treated daily with 67.5, 135 or 270 mg propachlor/kg body weight on days 1-7 or 8-16 of gestation (six test groups of 10 animals each). In a second set of experiments, a daily treatment of 33.7, 67.5, 135 and 270 mg/kg body weight was given throughout the gestation period (1-21 days) (Mirkova, 1975). Propachlor induced embryotoxicity at all dose levels of repeated treatment during the pre-implantation stages of embryogenesis (days 1-7 of gestation). This was expressed as raised lethality and haemorrhages, predominantly in the head of the fetus, and reduced weight and cranio-caudal size. The effects were significantly reduced when administration was performed during the period of organogenesis (8-16 days). Propachlor showed low teratogenic activity, producing external malformations of the tail (short, curved tail), skeletal abnormalities (non-ossified parietal and occipital bones) and hydrocephalus, at all three dose levels during the pre-implantation stage (days 1-7 of gestation). A slight degree of internal hydrocephalus was observed with doses of 135 and 270 mg/kg on days 8-16 of gestation.

Using a similar treatment regimen, Ivanova-Chemishanska et al. (1975) reported similar changes. No embryotoxic or teratogenic effect was seen at a dose level of 10 mg/kg body weight given daily to rats throughout the pregnancy (Medved, 1977; Panshina, 1985).

Teratogenic effects of technical propachlor were assessed in pregnant Charles River COBS CD rats using a control and three treatment groups consisting each of 25 females (Schardein & Wahlberg, 1982). Propachlor (96.5% pure) levels of 20, 60 and 200 mg/kg body weight were administered orally by gavage as a single daily dose on days 6-19 of gestation in a constant volume of 10 ml/kg corn oil. The control group received the same dose of corn oil. Survival in the control, low-dose and mid-dose groups was 100%. One female in the high-dose group died on gestation day 18 due to an intubation error. There were no differences in mean maternal body weight gain. No changes were evident at gross necropsy that could be considered treatment related. There were

no differences between treated and control groups with respect to the mean number of viable fetuses, post-implantations loss, total implantations, corpora lutea, fetal body weights, sex ratio distribution, and in the number of litters or fetuses with external, visceral or skeletal malformations and/or developmental and genetic variations.

7.4.2.2 Mice

When Balb/c mice (8-12 in each test group and 18 control pregnant females) were treated with a single dose of 675 mg propachlor/kg body weight on each of days 8-13 of gestation, and at dose levels of 33.7, 67.5, 135 and 270 mg/kg body weight per day from days 1 to 21, a significant increase in post-implantational lethality and reduced fetal weight and cranio-caudal size were observed at all dose regimens. With both single and repeated doses, there was a statistically significant increase in the frequency of internal hydrocephalus, but only at a dose level of 675 mg/kg in a single application on days 9 and 11 of gestation and on daily application at 270 mg/kg from days 1 to 18 of pregnancy (Mirkova, 1975).

7.4.2.3 Rabbits

Pregnant New Zealand White rabbits randomly assigned to a control and three treatment groups (each consisting of 16 rabbits) were used to determine the teratogenic potential of propachlor (95.6% pure) (Schardein, 1982). Dose levels of 5, 15 and 50 mg/kg were administered orally by gavage as a single daily dose on days 7-19 of gestation at a constant volume (0.5 ml/kg dissolved in corn oil). The control group received only 0.5 ml/kg corn oil. On gestation day 29, the number and location of viable and non-viable fetuses, early and late resorptions, number of total implantations and the number of corpora lutea were recorded. All fetuses were examined for external, soft tissue and skeletal malformations and for genetic or developmental variations.

Mortality (between 3 and 26 days of gestation) was recorded in the control as well as the treated groups, i.e. two in the control group, three at 5 mg/kg, three at 15 mg/kg and two at 50 mg/kg. Two rabbits from the low-dose group and one from the mid-dose group aborted on gestation days 22 to 25. Ante-mortem observations gave no indication of a treatment-related effect at any dosage level.

Results of the reproductive parameters revealed slight to moderate increases in the number of post-implantation losses and the number of early resorptions in the mid- and high-dose groups when compared with controls (Table 13). Single animals with resorptions only were also found at the two highest dose levels. This resulted in a subsequent decrease in the average number of viable fetuses in the mid- and high-dose groups when compared with controls. Although the number of post-implantation losses fell within the range of historical control frequencies, all the above parameters were considered to imply a mild embryotoxic response. No effects were observed in the number of late resorptions, total implantations, number of corpora lutea, fetal sex distribution or the mean fetal body weights. Examination of the fetuses revealed no external, skeletal or soft tissue malformations, or genetic and developmental variations that could be considered to be related to treatment. These abnormalities observed were low in frequency and within the range of historical control values. A statistically significant increase in the total number of litters with malformations was observed in the mid-dose group when compared to the control group. This trend, however, was not found in the high-dose group and the malformations in the group given 15 mg/kg per day were considered to be incidental to treatment.

Table 13. Mean number of resorptions (late and early), post-implantation losses and total implantations in New Zealand rabbits (Schardein, 1982)

Dose (mg/kg)	Fetuses		Resorptions		Post-implantation losses	Total implantations
	viable	non-viable	late	early		
0	8.0	0.0	0.3	0.3	0.6	8.6
5	7.9	0.0	0.0	0.4	0.4	8.3
15	5.2[a]	0.1	0.0	1.4	1.4	6.6
50	5.9	0.0	0.2	0.9	1.1	7.0

[a] $P < 0.05$

7.5 Mutagenicity and related end-points

Appraisal

Many in vitro *and* in vivo *studies on the genotoxicity of propachlor have been reported. It has been found to be clastogenic in* in vivo

lower test systems and plant assays. It is cytotoxic and also shows a weakly positive clastogenic response in in vitro *mammalian tests, inducing chromosomal aberrations in Chinese hamster ovary cells. Variable results do not allow any definite conclusions to be drawn. However, on the basis of negative results in many* in vivo *assays in mammalian test systems, the available experimental data provide insufficient evidence of a mutagenic potential. Data on mutagenicity testing are summarized in Table 14.*

7.5.1 Bacterial test systems

Salmonella mutation assays using standard tester strains (TA1535; TA1538; TA98 and TA100), both with and without metabolic activation with rat liver S9, were negative for formulations and technical grades of propachlor (Plewa et al., 1984; Flowers, 1984). No mutagenicity was observed with extracts of plants treated with propachlor.

Negatives results for propachlor in spot tests using *Salmonella typhimurium* test strains were also reported by Njagi & Gopalan (1980) and Eisenbeis et al. (1981).

7.5.2 Yeast assays

Propachlor was not recombinogenic when tested at 1000 mg/litre in *Saccharomyces cerevisae* strain D4 (ade 2-1, ade 2-2; trp 5-12, trp 5-27) either with or without a liver microsomal activation system (Gentille et al., 1977).

Extracts of plants treated with propachlor cause a weak recombinogenic activity (Gentille et al., 1977). Maize extracts treated with 25 ppm propachlor increased the rate of mitotic gene conversion at the ade locus in *S. cerevisae* strain D4 approximately 4-fold over the control levels. Extracts of plants treated with a technical grade of propachlor (1.306×10^{-4} mol/litre) and formulated grade (1.306×10^{-3} mol/litre) induced a significant increase in gene conversion at the ade locus and a lower increase at the trp locus in *S. cerevisae* D4. Results for both formulated and technical grades of propachlor were negative after mammalian S9 activation (Plewa et al., 1984).

7.5.3 Plant assays

Njagi & Gopalan (1981) studied the cytogenic and cytological effects of propachlor at a wide range of concentrations (10, 50,

Table 14. Summary of mutagenicity testing

Test material[a]	Test system	Result[c]			Reference
		-S9	+S9	1S	
Gene mutation in Prokaryotes					
Propachlor U	Ames spot test	-			Njagi & Gopalan (1980)
Propachlor U	Ames spot test	-	-		Eisenbeis et al. (1981)
Propachlor T	Ames plate test	-	-		Flowers (1984)
Propachlor T	Ames plate test	-	-	-	
Propachlor + Cyanazine[b]	Ames plate test			+	Plewa et al. (1984)
Gene mutation in plants					
Propachlor C	maize Wx locus	-			Plewa et al. (1984)
Gene mutation in mammals (*in vitro*)					
Propachlor T	CHO/HGPRT	-	-		Flowers (1985)
Chromosome effects in plants					
Propachlor U	*Vicia faba* cytogenetics	+			Njagi & Gopalan (1981)
Propachlor U	maize cytogenetics	+			Lapina et al. (1984)
Propachlor U	maize chlorophyll mutations	+			Lapina et al. (1984)

Table 14 (contd).

Test material[a]	Test system	Result[c] -S9	Result[c] +S9	Result[c] 1S	Reference
Chromosome effects in mammals (*in vitro*)					
Propachlor T	CHO cytogenetics	-	+		Li & Meyers (1987)
Chromosome effects in mammals (*in vivo*)					
Propachlor U	*in vivo* mouse bone marrow cyt.	+			Pilinskaya et al. (1980)
Propachlor T	*in vivo* rat bone marrow cyt.	-			Ernst & Blazak (1985)
DNA damage/recombination in yeast					
Propachlor T	gene conversion	-		+	Gentile et al. (1977)
Propachlor T	gene conversion	-	-	+	Plewa et al. (1984)
Propachlor C	gene conversion	-	-	+	Plewa et al. (1984)
Propachlor + Cyanazine	gene conversion			-	Plewa et al. (1984)
DNA damage in mammals (*in vitro*)					
Propachlor T	*in vitro* hepatocyte UDS	-			Steinmetz & Mirsalis (1984)
Propachlor T	*in vivo/in vitro* hepatocyte UDS	-			Steinmetz & Mirsalis (1986)

[a] T = technical grade; C = commercial grade; U = unspecified grade
[b] Propachlor and cyanazine were both of commercial grade.
[c] +S9 and -S9 = with or without rat liver S9 activation mixture; 1S = with maize 1S fraction

100, 500, 1000, 5000 and 10 000 ppm) in root-tip meristematic cells of *Vicia faba*. At a concentration of 100 ppm, propachlor induced, within 2 h, chromosomal aberrations, such as anaphase bridge formation, micronuclei as well as inhibition of mitosis, formation of highly pycnotic nuclei and premature chromosome condensation. The mutagenic properties of propachlor were not detectable in the field experiments using reverse mutations at the wx-C locus in maize as the genetic end-point. Lapina et al. (1984) also reported that propachlor induced mitotic chromosomal aberrations in the root-tip meristematic cells of an inbred F_2 strain of maize. At a concentration of 10^{-3} mol/litre and within 2 h of treatment of maize grains, propachlor increased the rate of mitotic chromosomal aberrations more than 4-fold over the control levels. The main types of cytogenetic damage included single bridges (72%) and fragments (28%). Propachlor did not show evidence of being significantly cytotoxic.

7.5.4 *Cultured mammalian cell CHO/HGPRT assay*

Propachlor (96.1%) was tested in a gene mutation assay in cultured mammalian cells (CHO/HGPRT assay), both in the presence and absence of mammalian metabolic activation, at doses ranging from 10-60 mg/litre. It was found to be cytotoxic at some of the higher concentrations tested, but no mutagenicity was observed (Flowers, 1985).

7.5.5 In vitro *unscheduled DNA synthesis in primary rat hepatocyte cultures*

Steinmetz & Mirsalis (1986) studied the potential of propachlor to induce unscheduled DNA synthesis (UDS) in primary rat hepatocyte cultures. They used ten concentrations of propachlor (95.8% pure) ranging from 0.1 to 5000 mg/litre and, in another assay, five concentrations ranging from 0.1 to 50 mg/litre. Results of this study showed a cytotoxic effect of propachlor at concentrations of 50 mg/litre or more, but there was no evidence of UDS induction.

7.5.6 In vitro *test for induction of chromosomal aberrations using Chinese hamster ovary cells*

Propachlor was tested for its potential to induce chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells treated with propachlor (97.4% pure) at concentrations of 5, 10 or 15 mg/litre for 5 h both in the presence and absence of exogenous activation (Li & Meyers, 1987). As indicated both by decrease in

mitotic index and lengthening of average cell generation times, the highest treatment level was cytotoxic both in the presence and absence of activation. In the non-activated study, no statistically significant increases in the percentage of cells with structural aberrations or in average structural aberrations per cell were observed at any treatment level. In the study with S9 activation (15 mg propachlor/litre), the average number of aberrations per cell was statistically elevated at 12 h and 24 h ($P < 0.05$ test). Chromatid and chromosome gaps were not included. The percentage of cells with structural aberrations following treatment at 15 mg/litre was statistically elevated at 12 h but not at 24 h. No apparent dose-response relationship was observed at either harvest time. Under these conditions, propachlor was considered to be negative in the assay without exogenous metabolic activation and a weak clastogen with activation.

7.5.7 In vivo *rat bone marrow cytogenetic assay*

Ernst & Blazak (1985) conducted an *in vivo* rat bone marrow cytogenetic assay using technical grade propachlor (95.6% pure) at dose levels of 0, 0.05, 0.2 and 1 mg/kg body weight. The results were evaluated for mitotic index (based on at least 1000 cells per animal) and 60 cells per animal were examined for chromosomal aberrations. Chromatid and isochromatid gaps were recorded for each cell, but these were not considered chromosomal aberrations. The results showed that propachlor does not induce chromosomal damage in male or female Fischer-344 rats under the conditions used in this study.

7.5.8 *Acute* in vivo *mouse bone marrow cytogenicity assay*

Pilinskaya et al. (1980) studied the cytogenetic effect of propachlor on the bone marrow of mice treated orally with 10, 50 and 100 mg/kg body weight. The metaphase frequency of aberration at the lowest dose applied was 2.67 ± 0.66 compared with 0.7 ± 0.19 in the control. At this dose level an approximately 4-fold increase in the frequency of chromosome aberrations was observed. No statistically significant changes were found at a dose level of 1 mg/kg.

7.5.9 In vivo/in vitro *hepatocyte DNA repair assay*

Steinmetz & Mirsalis (1986) presented data on the *in vivo/in vitro* hepatocyte DNA repair assay. Propachlor (97.7% pure) was suspended in corn oil and administered by gavage to five groups

of male Fischer-344 rats at dose levels of 25, 250, 300, 400 and 1000 mg/kg. A positive control group received 2-acetyl aminofluorene (2-AAF) (50 mg/kg) while a negative one was given corn oil. The results were negative.

7.6 Long-term toxicity and oncogenicity studies

7.6.1 Rat

Propachlor (96% pure) was administered via the diet to four groups of 60 male and 60 female Charles River CD SDBR rats at concentrations of 0, 10, 50 and 500 mg/kg (equivalent to 0, 0.5, 2.6 and 27 mg/kg body weight) (Hamada, 1987a). A complete battery of haematological, clinical chemistry and urinalysis tests was carried out every 6 months for 2 years. No treatment-related effects were noted on survival, incidence of clinical and ophthalmoscopic observations, body weight gain or food consumption. Haematological and clinical chemistry parameters and urinalysis data of treated animals were comparable to control values. Thyroid and liver weights were slightly increased in high-dose males at the 12-month interim sacrifice but not at the end of the study. An increased incidence of liver changes (centrilobular hypertrophy, clear cell cytoplasmic alteration and eosinophilic cytoplasmic alteration) was observed in high-dose males and females. A slightly higher incidence of thyroid c-cell tumours (adenomas and carcinomas) noted in high-dose animals was within the testing laboratories' historical range for such tumours. All other organ weight changes and gross and microscopic pathological findings were comparable to controls. An increase in benign granulosa/theca cell tumours was observed for high-dose females (4/60) compared to controls (0/60). The historical control data for this tumour ranged from 0/80 to 4/96. On the basis of these results, 50 mg/kg diet (2.6 mg/kg body weight) can be considered the no-observed-effect level (NOEL) for rats.

7.6.2 Mouse

When propachlor (96.1% pure) was administered in the diet to male and female CD1 mice at dose levels of 10, 50 and 500 mg/kg (equivalent to 1.6, 8.1 and 81.3 mg/kg for males and 2.0, 10.5 and 104.9 mg/kg for females) for 18 months, no histological changes were noted (Hamada et al., 1987b). The survival of all treated male groups was similar to that of controls. Female survival was lower than that of controls in all treated groups. There was a significant increase in segmented neutrophilic leucocytes in the

500-mg/kg group at 12 months, but this change was not evident at study termination. At the end of the study, ratio of liver (with gall bladder) to body weight was increased in the 50- and 500-mg/kg group females, and the ratio of kidney to body weight was decreased in males of the highest-dose group. The NOEL was considered to be 10 mg/kg (1.6 mg/kg per day).

7.6.3 Dog

In a study by Naylor & Ruecker (1986), propachlor was administered daily via the diet to four groups of six male and six female beagle dogs for 12 months (0, 25, 250 and 1000 mg/kg diet). No mortality occurred during the study. Absolute body weights were lower than those of controls at study termination (approximately 14% for males and 8% for females in the high-dose group and 5% for males in the mid-dose group. A slight increase in emesis and/or stool change was noted in treated dogs. No other changes in clinical and pathological parameters were observed that could be related to treatment. Based on the body weight depression at the high dose, a dietary level of 250 mg/kg (9 mg/kg body weight) was considered a no-observed-adverse-effect level (NOAEL) in this chronic study.

7.7 Miscellaneous studies

Propachlor has a strong inhibitory effect on the proliferation of L1210 mouse leukaemia cells *in vitro* (the ID_{50} for cell proliferation is $< 3 \times 10^{-7}$ mol/litre). Propachlor also inhibits significantly the uptake of leucine, thymidine and uridine. The inhibitory effect of propachlor is largely reversible, i.e. cells grown in propachlor and then washed free of the compound return to an almost normal rate of proliferation (Zilkah et al., 1981).

It has been demonstrated that propachlor treatment also causes L1210 cells to accumulate in the G1 phase. This effect is dose dependent; a concentration of 10 µmol/litre causes more than 90% of cells to accumulate in the G1 phase (Zilkah et al., 1985).

The combined effect of propachlor and vibration has been studied. Propachlor was given orally to Wistar rats (20 animals in each group) at doses equivalent to 6, 12 and 60 mg/kg body weight per day for 3 months, and the animals were exposed to low-frequency vibration (15 Hz) during the last 30 days of the study. The results were compared with those obtained from groups of rats subjected to the effect of 15 Hz vibration daily for 30 days,

as well as with those of groups of rats dosed only with propachlor. It was found that the combined exposure (with 12 or 60 mg propachlor/kg) caused more severe haemodynamic alterations and degenerative (even necrotic) changes in the epithelial cells of the renal tubules, either in the proximal or distal convoluted tubules (Maleva & Zlateva, 1982).

In a study by Baynova et al. (1978b), groups of 20 white rats were pretreated with oral doses of 4 ml/kg 40% ethanol (one tenth of the LD_{50}), 6 days per week, for 4 months. Propachlor was then given daily at a dose level of 140 mg/kg (one tenth of the LD_{50}), 6 days per week, every other week for a further 4-month period. The controls were subjected to 8 months of treatment with ethanol and 4 months of intermittent (every second week) treatment with propachlor using the same doses as in the combined experiment. Both experiments had untreated control groups. The combined treatment led to a reduction of the hepatotoxic effect. This was probably due to induction of mixed-function oxidases and to a more rapid biotransformation in the hepatocytes. It has also been found that propachlor (140 mg/kg for 6 days) reduces the hexabarbital sleeping time by speeding up its metabolism in the hepatic endoplasmic reticulum as a result of induction of the mixed-function oxidase system in the liver cell microsomes (Nenov & Baynova, 1978).

8. EFFECTS ON HUMANS

8.1 Occupational exposure

There have been few reports dealing with the effects of propachlor on humans.

Von Schubert (1979) reported a case of contact eczema on the palms, wrists and forearms of a 29-year-old agricultural worker who had been in contact with propachlor for 8 days. Once this contact ceased, the skin lesions disappeared.

Iden & Schroeter (1977) patch-tested 17 patients, predominantly farmers, who had been exposed simultaneously to many types of herbicides. Seven showed a positive patch test reaction and five others had an irritant reaction to propachlor. One of these farmers, who was highly sensitive to propachlor, used to develop generalized airborne contact dermatitis each spring when his neighbours used this product. Farkasdy et al. (1976) and Dombay & Farkasdy (1978) examined dermatologically 79 workers manufacturing Satecid 65 WP (65% propachlor). Of these, 19% showed contact dermatitis attributed to propachlor exposure. Patch testing was carried out on 67 workers of this group, 12 of whom showed monovalent and bivalent hypersensitivity reaction to propachlor. Photosensitization tests were negative in 28 of the cases tested. Three years later, the same authors examined 108 workers who were continuously exposed to Satecid in the same factory without finding any sign of sensitization.

Jung et al. (1989) patch-tested 19 allergic cases and one irritative case with occupational contact eczema, who were exposed to different types of herbicides. Two of them showed positive testing to Satecid 65 WP. One of these two was only exposed to the substance for 10 days and the other for 6 months.

8.2 General population exposure

No reports on general population exposure are available.

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

9.1 Microorganisms

9.1.1 Soil

The effects of propachlor with regard to changes in numbers of four types of soil bacteria (aerobic nitrogen-fixing, aerobic cellulose-decomposing, ammonifying and nitrifying) was studied by Helmeczi (1977). The studies were carried out using pseudomycelial chernozem soil with maize plants. For the purpose of the microbial examinations, samples from the field were taken three times a year (after spraying propachlor in spring, summer, and autumn at a rate of 8-10 kg/ha) from the upper 20-cm layer of the soil. Sampling was carried out under sterile conditions and samples were collected in sterile vessels. The nitrifying bacteria had the greatest sensitivity to propachlor, their number decreasing considerably from 2720 to 610 per g soil in 1974 and from 4510 to 1920 per g soil in 1975. The aerobic cellulose-decomposing bacteria were the least sensitive, their numbers, with respect to the control bacteria, increasing to a small extent.

Long-term studies in smolnista and alluvial soils have been carried out to establish the effects of propachlor on useful soil microorganisms and the processes of nitrification (Bakalivanov & Kostov, 1981). These studies were conducted under laboratory conditions at 20 °C and 60-70% soil moisture for a period of 10 days. The concentration of propachlor used was 80 mg/kg soil. The results showed an inhibitory effect on nitrification and weaker effect on soil microorganisms (bacteria, actinomycetes and microscopic fungi). High adsorption of propachlor to clay minerals reduced the toxic effect on microorganisms.

Rankov & Velev (1976) studied the effect of propachlor on the biological activity of soil microorganisms and showed that inhibition was greater at a temperature of 2 to 4 °C than at 20 to 22 °C.

9.1.2 Water

The acute toxicity of propachlor to *Selenastrum capricornutum* Printz has been assessed in two studies. In the first (Richards & Kaiser, 1984), the 96-h EC_{50} for growth in algae was calculated to

be 0.029 mg/litre with 95% confidence intervals of 0.021–0.038 mg/litre. The no-observed-effect concentration (NOEC) was calculated to be 0.01 mg/litre. In the second study (Zschaler & Jonas, 1990), the 72-h EC_{50} for growth was 5.3 mg/litre and the NOEC 1.9 mg/litre for a propachlor formulation containing 65% active ingredient. The differences in toxicity observed between the two studies may be either because the 65% formulation is less toxic than technical propachlor or because the duration of the second study was 24 h shorter.

9.2 Aquatic organisms

9.2.1 Aquatic invertebrates

Thompson & Forbes (1979a) determined a 24-h LC_{50} of 11 mg/litre and a 48-h LC_{50} of 7.8 mg/litre for the water flea *Daphnia magna*. The NOEC in this study was < 5.6 mg/litre. A 48-h LC_{50} of 6.9 mg/litre in the same species was reported by Mayer & Ellersieck (1986). The same authors reported a 48-h LC_{50} of 0.79 mg/litre for the midge larva *Chironomus plumosus*. Another midge larva *Chironomus riparius* was reported to show a 24-h LC_{50} of 5.2 mg/litre and a 48-h LC_{50} of 1.8 mg/litre (Buhl & Faerber, 1989).

The effects of propachlor on daphnia reproduction was assessed in a 21-day life-cycle study (Thun, 1990a). In this study, there was decreased reproductive performance at concentrations from 0.29 to 2.6 mg/litre; the NOEC for reproduction was considered to be 0.097 mg/litre.

9.2.2 Fish

Thompson & Forbes (1979b) determined 24-h, 48-h and 96-h LC_{50} values for rainbow trout (*Onchorynchus mykiss*) of 0.75, 0.28 and 0.17 mg/litre, respectively. Thun (1990b) conducted a 21-day study on rainbow trout and found that fish died at concentrations between 0.11 and 0.3 mg/litre. No deaths related to exposure occurred at concentrations between 0.009 and 0.075 mg/litre. The NOEC was considered to be 0.019 mg/litre. Mayer & Ellersieck (1986) reported a 96-h LC_{50} of 0.23 mg/litre for the channel catfish (*Channa punctatus*).

9.3 Terrestrial organisms

9.3.1 Terrestrial invertebrates

The toxicity of propachlor to earthworms was assessed in a 14-day study (Thun et al., 1991). Propachlor (97.8% pure) was added to the soil at five concentrations ranging from 100 to 1000 mg/kg, and 40 worms were added to the soil at each concentration. Worms were removed from the soil at 7 and 14 days and examined for any adverse effects. Body weights were measured at the beginning and end of the test. The LC_{100} was 560 mg/kg and the LC_0 218 mg/kg; the NOEC was 100 mg/kg.

The contact LD_{50} of propachlor for honey bees was reported to be 311 μg/bee (Kenaga, 1979).

Under laboratory conditions, Tanke & Franz (1978) studied the side effects of propachlor on some beneficial insects by measuring the reduction of the beneficial capacity of three enthomophagous insects. The egg parasite *Trichogramma cacoeciae* March reacted very strongly in laboratory as well as in field conditions to the effects of the herbicide. Contact toxicity tested using residues of propachlor on glass plates (residue level not stated) caused a reduction of the degree of parasitization leading to total mortality of the population in contaminated cages. In a study on the contact toxicity of the spray deposit on single leaves as well as on whole plants, the parasitization of *Trichogramma* was reduced by 100 and 83%, respectively. The direct toxic effect should be distinguished from a repellent effect, which is probably more important in the field. In addition to this direct contact effect of spray deposits, systemic application also caused an effect after transport of the herbicide through the soil and the plant. This was demonstrated by a reduction of the degree of parasitization compared with untreated controls.

Propachlor does not seem to have any influence on *Chysopa carnea* Steph larvae. No effect was visible either in tests of contact toxicity or contaminated sandy soil, in choice studies on a repellent action of the residue or after topical application of the preparation. After oral application through an artificial food chain, no influence could be demonstrated. Only overdosage increased the mortality rate of the test larvae. No repellent effect of the herbicide on adults was demonstrated (Tanke & Franz, 1978).

The syrphid *Epistrophe balteata* DeG was more sensitive. Both in contact toxicity studies and in studies for a possible repellent effect, an influence of propachlor on the larval stages was shown. Oral intake through an artificial food chain did not have an effect on the larvae. When the herbicide was sprayed directly on the plant, an increase in larval mortality was observed. Adults of this syrphid also showed reactions to herbicides; during egg deposition, females avoided surfaces previously treated (Tanke & Franz, 1978).

The potential toxicity of a 65% formulation of propachlor to *Aleochara bilineta* Gyll was assessed by Pietrzik (1991). The imagos were dug into moist sand and the test substance was added at recommended use rates (8 kg in 400 litres/ha water). For the assessment of parasitical capacity, pupae of *Delia antiqua* were dug into the sand. At the termination of the test, the sum of hatched *Aleochara* larvae in the pupae was determined. These were compared to the number of control organisms treated with tap water. The parasitic capacity of the test beetles was decreased by 11.4% when compared to controls.

9.3.2 Birds

Palazzolo (1964) reported data for pheasants indicating an acute oral LD_{50} of 735 mg/kg body weight. Increased respiration, loss of reflexes, mydriasis, salivation and intermittent tonic/clonic convulsions were found among birds receiving dose levels of 900 and 1350 mg/kg. The onset of symptoms occurred approximately 15 min following dosing and persisted until death 3-5 h later. Kenaga (1979) reported an LD_{50} of 512 mg/kg for Mallard duck and Beavers & Fink (1979) reported an LD_{50} for Bobwhite quail of 137 mg/kg body weight for a 65% propachlor formulation.

When propachlor was administered in the diet to quail or Mallard ducks for five consecutive days, the LC_{50} for both species of birds was more than 5620 mg/kg diet (Beavers & Fink, 1983a,b). For the quail, a dietary level of 5620 mg/kg is approximately equivalent to a dose of 1400 mg/kg per day. The data presented above indicate that the quail is more susceptible to exposure to propachlor via stomach tube than via the diet.

10. CONCLUSIONS AND RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

10.1 Conclusions

- Under conditions of normal use, the general population is not likely to be exposed to propachlor.

- Those occupationally exposed to propachlor should take adequate safety and hygienic precautions in order to protect the skin, eye and respiratory tract.

- Propachlor is rapidly degraded in the environment under most conditions. It persists longer in cold dry environments. The conjugated *N*-isopropylaniline metabolite persists longer than the parent compound. Propachlor does not bioconcentrate or biomagnify.

- Propachlor is highly toxic to some aquatic organisms. Exposure of aquatic organisms under conditions of normal use is low, the maximum expected concentrations being several orders of magnitude lower than the no-observed-effect concentrations. Direct contamination of water courses will kill aquatic organisms and should be avoided. Propachlor poses a low hazard to birds, earthworms and honey-bees.

10.2 Recommendations for protection of human health

Workers should be educated about the hazards of propachlor and systematically trained to practice safety and personal hygiene and to use protective equipment.

11. FURTHER RESEARCH

- The results of the existing animal studies on mutagenicity are inconclusive and more research is needed.
- Studies should be performed in laboratory animals to determine the potential neurotoxic effects of propachlor.
- Only validated analytical methods for residues of propachlor should be used.
- Epidemiological studies on occupationally exposed workers are needed.
- There is a need to develop methods of biological monitoring for evaluating human exposure to propachlor.
- Research is needed to clarify the exposure of workers in the production and agricultural use of propachlor. Studies should also include examination of health effects at the measured exposure levels.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

In the WHO recommended classification of pesticides by hazard, technical propachlor is classified in Class III as slightly hazardous in normal use (WHO, 1990). A data sheet on propachlor has been issued (WHO/FAO, 1989).

Neither the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) nor the International Agency for Research on Cancer (IARC) has so far evaluated propachlor.

REFERENCES

Aschbacher PW & Struble CB (1987) Evidence for involvement of non-biliary excretion into the intestine of the formation of methyl-sulphonyl containing metabolites of 2-chloro-N-isopropylacetanilide (propachlor) by swine and rats. Xenobiotica, **13**(2): 115-126.

Auletta CS (1983) A propachlor dermal sensitization study in guinea-pigs (Project No. 4236-83). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Auletta CS (1984) Eye irritation study with propachlor in rabbits (Project No. 5050-84). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Auletta CS & Rinehart WE (1979) Acute dermal toxicity study in rabbits (Project No. 4892-77). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report submitted to WHO by Monsanto Agricultural Services, Brussels).

Auletta CS, Erickson J, & Webb M (1984a) A closed-patch repeated insult dermal sensitization study in guinea-pigs (modified Buehler method) (Project No. 4946-84). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Auletta CS, Erickson J, & Webb M (1984b) A closed-patch repeated insult dermal sensitization study in guinea-pigs (modified Buehler method) (Project No. 4540-83). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Bakalivanov D & Kostov O (1981) Soil microbiological assessment of toxicity of alkanoate, amide, and other herbicides. Acta microb Acad Sci Hung, **28**: 141-146.

Baker JL (1980) Agricultural areas as non-point sources of pollution. In: Overcash MR & Davidson JM ed. Environmental impact of non-point source pollution. Ann Arbor, Michigan, Ann Arbor Science Publishers, pp 275-310.

Baker JL & Laflen JM (1979) Run-off losses of surface applied herbicides as affected by wheel tracks and incorporation. J Environ Qual, **8**(4): 602-607.

Baker JL, Laflen JM, & Hartwig RO (1982) Effects of corn residue and herbicide placement on herbicide run-off losses. Trans Am Soc Anal Eng, **25**(2): 340-343.

Bakke JE, Gustafsson JA, & Gustafsson BE (1980) Metabolism of propachlor by the germ-free rat. Science, **210**: 433-435.

Bakke JE & Price CE (1979) Metabolism of 2-chloro-N-isopropylacetanilide (propachlor) in the rat. J Environ Sci Health, **B14**(4): 427-441.

Bakke JE, Davison KL, & Larsen GL (1990) Evidence for the absence of cysteine S-conjugate N-acetyltransferase activity in the metabolism of propachlor, naphthalene, and dichlobenil in calves. Xenobiotica, **20**: 801-807.

Bakke JE, Rafter J, Larsen GL, Gustafsson JA, & Gustafsson BE (1981a) Enterohepatic circulation of the mercapturic acid and cysteine conjugates of propachlor. Drug Metab Dispos, **9**(6): 525-528.

Bakke JE, Rafter J, Lindeskog P, Feil V, Gustafsson JA, & Gustafsson BE (1981b) Metabolism of 2-acetamido-4-(chlormethyl) thioazole in germ-free and conventional rats. Biochem Pharmacol, **30**(13): 1831-1844.

Bakke JE, Larsen GL, Aschbacher PW, Rafter J, & Gustafsson JA (1981c) Role of gut microflora in metabolism of glutathione conjugates of xenobiotics. In: Rosen JD, Magee PhS, & Casida JE ed. Sulfur in pesticide action and metabolism. Washington, DC, American Chemical Society, pp 165-178 (ACS Symposium Series No. 158).

Balinova AM (1981) Investigations in the residues of some herbicides in plant production in view of its hygienic evaluation. Sofia, University of Sofia (Dissertation).

Balinova A & Konstantinov K (1975) Investigations on residues of several herbicides in vegetables. In: Proceedings of the COMECOM Symposium on Residues of Herbicides in Plants and Soils, Vrozlav, 1973, pp 111-116.

Barrows ME & Macek KJ (1974) Exposure of fish to ^{14}C-Ramrod™: Accumulation, distribution and elimination of ^{14}C-residues. Wareham, Massachusetts, Bionomics, E.G. & G. Inc., 18 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Baynova A, Burkova T, & Michailova A (1977) [Determination of dermal toxicity of Ramrod.] Gig Zdraveopazvane, 20(3): 234-240 (in Russian).

Baynova A, Burkova T, & Michailova A (1978a) [Comparative study on intermittent and monotonous effects of the herbicide Ramrod.] Gig Zdraveopazvane, **21**: 568-573 (in Russian).

Baynova A, Krastev L, Dikova M, & Michailova JA (1978b) Effect of alcohol on acute and chronic intoxication with the herbicide Ramrod. Acta med Bulg, **2**: 36-41.

Beavers JB & Fink R (1979) Acute oral LD_{50}-Bobwhite Quail. Propachlor report No. WL-79-026. Easton, Maryland, Wildlife International Ltd (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Beavers JB & Fink R (1983a) Eight-day dietary LC_{50} - Bobwhite Quail propachlor. Easton, Maryland, Wildlife International Ltd (Unpublished proprietary report No. WL-83-90, submitted to WHO by Monsanto International Services, Brussels).

Beavers JB & Fink (1983b) Eight-day dietary LC_{50} - Mallard Duck propachlor. Easton, Maryland, Wildlife International Ltd (Unpublished proprietary report No. WL-83-89, submitted to WHO by Monsanto International Services, Brussels).

Bechtel CL (1991) Acute inhalation study of propachlor Technical (Project No. ML-91-2). Newstead, St. Louis, Monsanto Environmental Health Laboratory (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Beestman GB & Deming JM (1974) Dissipation of acetanilide herbicides from soils. Agron J, **66**: 306-311.

Blaszcak DL (1988) A comparative acute oral toxicity study in Sprague-Dawley and Fischer rats (Project No. 4359-87). East Millstone, New Jersey, Bio/dynamics Inc., 37 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Bleeke MS, Carr KH, & Elliot RC (1987) Propachlor metabolism in the laying hen (Project No. MSL-6217). St. Louis, Missouri, Monsanto Agricultural Company, 134 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Branch DK, Stout LD, & Folk RN (1982a) Acute oral toxicity of Ramrod® 4L flowable herbicide for rats (Project No. ML-81-182). Newstead, St. Louis, Monsanto Environmental Health Laboratory (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Branch DK, Stout LD, & Folk RN (1982b) Primary skin irritation of Ramrod® 4L flowable herbicide to rabbits (Project No. 810096). Newstead, St. Louis, Monsanto Environmental Health Laboratory (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Braun WG (1979) Rabbit eye irritation study (Project No. 4889-77). East Millstone, New Jersey, Bio/dynamics Inc., 4 pp (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Braun WG & Rinehart E (1978) Acute dermal toxicity study in rabbits (Project No. 4888-77). East Millstone, New Jersey, Bio/dynamics Inc., 4 pp (Unpublished proprietary report, submitted to WHO by Monsanto International Services, Brussels).

Braun WG, Heenehan PR, & Rinehart WE (1979a) Primary dermal irritation study in rabbits (Project No. 4890-77). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Braun WG, Heenehan PR, & Rinehart WE (1979b) Primary dermal irritation study in rabbits (Project No. 4898-77). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Braun WG, Heenehan PR, & Rinehart WE (1979c) Primary dermal irritation study in rabbits (Project No. 4894-77). East Millstone, New Jersey, Bio/dynamics Inc. (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Brightwell BB & Rueppel ML (1976) Lasso® and Ramrod®: physical properties and their relationship to the environment. St. Louis, Missouri, Monsanto Agricultural Company (Unpublished report No. 443, submitted to WHO by Monsanto International Services, Brussels).

Brightwell BB, Malik JM, & Wong SC (1981) The environmental fate of propachlor [2-chloro-N (1-methyl)-N-phenyl-acetamide] in soil and water. St. Louis, Missouri, Monsanto Research Laboratory, 1300 pp (Unpublished proprietary report No. MSL-1900, submitted to WHO by Monsanto International Services, Brussels).

Buhl KJ & Faerber NL (1989) Acute toxicity of selected herbicides and surfactants to larvae of the midge *Chironomus riparius*. Arch Environ Contam Toxicol, **18**: 530-536.

Caverly DJ & Denney RC (1978) Determination of substituted ureas and some related herbicide residues in soils by gas chromatography. Analyst, **103**: 368-374.

Daly I & Knezevich A (1984) Four-week toxicity study in dogs (Bio/dynamics Inc. Project No. 84-2798). Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels.

Davison KL (1991) Propachlor-s-glutathione metabolism by kidneys and ureters of calves. J Anim Sci, **69**: 1116-1121.

Davison KL, Bakke JE, & Larsen GL (1988) A kidney perfusion method for metabolism. Studies with chickens using propachlor as a model. Xenobiotica, **18**(3): 323-329.

Davison KL, Bakke JE, & Larsen GL (1990) Metabolism of the glutathione conjugate of propachlor by *in situ* perfused kidneys and livers of rats. Xenobiotica, **20**(4): 375-383.

Dombay Z & Farkasdy J (1978) [Problems of safety technique and of occupational safety as related to propachlor and its formulations.] In: [Conference on Safety Technology in the Application of Agricultural Chemicals], Budapest, Technoinform, pp. 49-58 (in German).

Eisenbeis SJ, Lynch DL, & Hampel AE (1981) The Ames mutagen assay tested against herbicides and herbicide combinations. Soil Sci, **131**(1): 44-46.

Ernst L & Blazak F (1985) An assessment of the mutagenic potential of propachlor utilizing the acute *in vivo* rat bone marrow cytogenetics assay (Project No. SR-84-180). Menlo Park, California, Stanford Research Institute, 39 pp. (Unpublished proprietary report, submitted to WHO by Monsanto International Services, Brussels).

FAO (1982) Second Government Consultation on International Harmonization of Pesticide Registration Requirements, Rome, 11-15 October 1982. Rome, Food and Agriculture Organization of the United Nations.

Farkasdy J, Horvath A, & Meszleri E (1976) [Occupational dermatitis caused by the selective herbicide Satecid 65WP.] Borgyogy venerol Sz, **52**: 112-118 (in German).

Feil VJ, Bakke JE, & Larsen GL (1981) A new metabolite of propachlor isolated from germ-free rat excreta. Biomed Mass Spectrom, **8**(1): 1-4.

Fletcher WW & Kirkwood RC (1982) Herbicide and plant growth regulators. London, Toronto, Sydney, New York, Granada.

Flowers LJ (1984) Salmonella mutagenicity assay of propachlor. Newstead, St. Louis, Monsanto Environmental Health Laboratory, 18 pp (Unpublished proprietary report No. MSL-1694, submitted to WHO by Monsanto International Services, Brussels).

Flowers LJ (1985) CHO/HGPRT gene mutation assay with propachlor. Newstead, St. Louis, Monsanto Environmental Health Laboratory, 9 pp (Unpublished proprietary report No. ML-84-237, submitted to WHO by Monsanto International Services, Brussels).

Frank R, Sirons GJ, Paik NJ, & Valk M (1977) Fate of propachlor applied to onions and organic soils. Can J Plant Sci, **57**: 473-477.

Gentille JM, Wagner ED, & Plewa MJ (1977) The detection of weak recombinogenic activities in the herbicides alachlor and propachlor using a plant activation bioassay. Mutat Res, **48**: 113-116.

Gustafson DI (1989) Groundwater ubiquity score: A simple method for assessing pesticide leachability. Environ Toxicol Chem, **8**: 339-357.

Hamada NN (1987a) Combined chronic toxicity and oncogenicity study in rats with propachlor (Study No. HL-83-350/241-169). Vienna, Virginia, Hazleton Laboratories America Inc., 2452 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Hamada NN (1987b) Oncogenicity study with propachlor in mice (Study No. HL-83-349/241-159). Vienna, Virginia, Hazleton Laboratories America Inc., 520 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Heenehan BS, Rinehart WE, & Braun WG (1979) Acute oral toxicity study in rats (Project No. 1895-77) (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Heise H, Mattheus A, & Pushkeiler TH (1983) [The irritant and allergic effect of the herbicidal agent propachlor.] Z Gesamte Hyg, **29**(11): 675-677 (in German).

Helmeczi B (1977) The effect of herbicides on soil bacteria belonging to certain physiological groups. Acta phytopathol Acad Sci Hung, **12**(1-2): 41-49.

Humburg NE, Colby SR, Lym RG, Prasad R, Hill ER, Kitchen LM, & McAvoy WJ (1989) Herbicide handbook, 6th ed. Champaign, Illinois, The Weed Science Society of America.

Iden DL & Schroeter AL (1977) Allergic contact dermatitis to herbicides. Arch Dermatol, **113**(7): 983.

Ivanova-Chemishanska L, Vergieva T, & Mirkova E (1975) Embryotoxic and teratogenic effects of some pesticides. Exp Med Morfol, **14**(1): 29-33.

Jung HD, Honemann W, Kloth C, Lubbe D, & Pambor M (1989) Contact eczema caused by pesticides in East Germany. Dermatol Monatschrift, **175**: 203-214.

Kaempfe BS (1991) Acute inhalation study of MON 15606 (Project No. ML-91-48). Newstead, St Louis, Monsanto Company Environmental Health Laboratory. (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Kenaga EE (1979) Acute and chronic toxicity of 75 pesticides to various animal species. Down Earth, **35**(2): 25-31.

Kofman IS & Nishko P (1984) Determination of micro-quantities of herbicides from a group of acetylanilides by thin-layer chromatography. Physiol Biochem Cult Plant, **16**(3): 290-292.

Kolesnikov VA, Abramova KA, & Grip OK (1979) Use of herbicides on white cabbage. Khim Sel'skom Khoz, **17**(10): 27-31.

Kolesnikov VA, Karetskaia NA, & Petuchova VI (1980) Efficacy of herbicides in garlic crop. Khim Sel'skom Khoz, **18**(8): 38-40.

Lamoureux GL & Davidson KL (1975) Mercapturic acid formation in the metabolism of propachlor, CDAA and Flurodifen in the rat. Pestic Biochem Physiol, **5**: 497-506.

Lamoureux GL & Rusness DG (1989) Propachlor metabolism in soybean plants, excised soybean tissues, and soil. Pestic Biochem Physiol, **34**: 187-204.

Lamoureux GL, Stafford LE, & Tanaka FS (1971) Metabolism of 2-chloror-N-isopropyl-acetanilide (propachlor) in the leaves of corn, sorghum, sugar cane, and barley. J Agric Food Chem, **19**(2): 346-350.

Lapina TV, Grigorenko NV, Morgun V, Logvinenko VF, & Merjinskii JG (1984) Study of the mutagenic effect of the herbicides Treflan, Ramrod, and Banvel on corn. Tsitol i Genet, **18**(2): 119-122.

Larsen GL & Bakke JE (1979) Studies on the origin of the methylsulfonyl-containing metabolites from propachlor. J Environ Sci Health, **B14**: 427.

Larsen GL & Bakke JE (1981) Enterohepatic circulation in formation of propachlor (2-chioro-N-N-isopropylacetanilide) metabolites in the rat. Xenobiotica, **11**(7): 473-480.

Larsen GL & Bakke JE (1983) Metabolism of mercapturic acid-pathway metabolites of 2-chloro-N-isopropylacetanilide (propachlor) by gastrointestinal bacteria. Xenobiotica, **13**(2): 115-126.

Larsen GL, Larsen JD, & Gustafson JA (1983) Cysteine conjugate beta-lyase in the gastrointestinal bacterium *Fusobacterium necrophorum*. Xenobiotica, **13**(11): 689-700.

Lee JK, Minard RD, & Bollag JM (1982) Microbial metabolism of propachlor in soil suspension. J Korean Agric Chem Saf, **25**(1): 44-53.

Lehotzky K, Szeberenyl JMS, & Tatrai E (1979) On the local and systematic toxic effects of the herbicide propachlor (Satecid 65WP) in experimental animals. Egeszegtudomany, **23**: 89-96.

Li AP & Meyers CA (1987) *In vitro* cytogenetics study of propachlor (Study No. MSL-6939), 24 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Lottman CM & Cowell JE (1986) Propachlor residues in processed sorghum grain applications following pre-emergent applications of Ramrod 4L herbicide (Project No. MSL 6091) (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Lottman CM & Cowell JE (1987) Propachlor residues in processed corn grain fractions following pre-emergent applications at Ramrod 4 h herbicide (Study No. MSL-6260) (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Magnusson B & Kligman AM (1969) The identification of allergens by animal assay. The guinea-pig maximalization test. J Invest Dermatol, **52**: 268-276.

Maleva E & Stereva M (1977) [Biochemical investigation on changes of gonads of male white rats under combined action of low frequency vibrations and intoxication with

Ramrod. I. Changes in the content of protein.] In: [Proceedings of the National Scientific Session of Chemists with Medical Direction, Part 2], pp. 306-313 (in Bulgarian).

Maleva E & Zlateva M (1982) Histomorphological changes in kidneys of experimental animals under the combined effect of low-frequency vibration and intoxication with Ramrod herbicide. Hig Zdraveopazvane, **25**(3): 244-249.

Malik JM (1982) Bioconcentration of propachlor in channel catfish under static conditions. Columbia, Missouri, Analytical Biochemistry Laboratories, 144 pp (Unpublished proprietary report No. 24242, submitted to WHO by Monsanto International Services, Brussels).

Malik JM (1986) Metabolism of propachlor in rats (Project No. 7815). St. Louis, Missouri, Monsanto Agricultural Company, Research Department (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Markus JR & Puma B (1973) Pesticide analytical manual. Volume II: Methods for individual pesticide residues. Springfield, Virginia, US Department of Commerce, National Technical Information Service, pp 1-7.

Martin CD, Baker JL, Erbach DC, & Johnson HP (1978) Wash-off of herbicides applied to corn residue. Trans Am Soc Anal Eng, **21**(6): 1164-1168.

Mayer FL Jr & Ellersieck MR (1986) Manual of acute toxicity: Interpretation and data base for 410 chemicals and 66 species of freshwater animals. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Resource Publication 160).

Medved LI (1977) [Manual of pesticides.] Kiev, K. Urojai (in Russian).

Melnikov NN, Novojilov KV, Belen SP, & Pilova TN (1985) [Manual of pesticides.] Moscow, M. Khimia (in Russian).

Menges RM & Tamez S (1973) Effect of soil incorporation on selectivity, movement, and persistence of herbicides in onion plantings. J Am Soc Hortic Sci, **98**(4): 390-393.

Mirkova E (1975) Embryotoxic and teratogenic action of pesticides Basfungin and Ramrod. Sofia, University of Sofia (Dissertation).

Molnar J & Paksy KA (1978) Acute inflammation of rat membranes evoked by eye-instillation and inhalation of pesticide formulations containing propachlor and TMTD. Egeszsegtudomany, **22**: 393-397.

Nadeau RG & Pantano LK (1986) Metabolism study of synthetic $^{13}C/^{14}C$-labelled plant metabolites of propachlor in lactating goats. Part II: Identification characterization and quantification of metabolites (Project No. MSL-5909), 119 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Naylor MW & Ruecker RW (1986) One-year dog study with propachlor (Study No. ML-84-379). Newstead, St. Louis, Monsanto Environmental Health Laboratory (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Nenov P & Baynova A (1978) Ramrod (propachlor) effect on the activity of rat hepatic microsomal enzymosystems. Acta med Bulg, **5**(2): 44-52.

Nesterova OA, Popova VV, & Kolesnikova OP (1980) [Accumulation of semeron, mesoranil, and Ramrod in the soil and cabbage during long-term use.] Sibirski Vestn S-Kh Nauki, 10(4): 19-21 (in Russian).

Njagi GDE & Gopalan HNB (1980) Mutagenicity testing of some selected food preservatives, herbicides, and insecticides. II. Ames test, Bangladesh. J Bot, 9(2): 141-146.

Njagi GDE & Gopalan HNB (1981) Mutagenicity testing of herbicides, fungicides, and insecticides. I. Chromosome aberrations in *Vicia faba*. Cytologia, 46: 169-172.

Novick NJ & Alexander M (1985) Co-metabolism of low concentrations of propachlor, alachlor, and cycloate in sewage and lake water. Appl Environ Microbiol, April: 737-743.

Novick NJ, Mukherjee R, & Alexander M (1986) Metabolism of alachlor and propachlor in suspensions of pretreated soil and in samples from ground water aquifers. J Agric Food Chem, 34: 721-725.

Palazzolo RJ (1964) Acute oral toxicity study on CP 31393 in Golden Ring-necked pheasants. Northbrook, Illinois, Industrial Biotest Laboratories (Unpublished proprietary report No. BLT-64-3, submitted to WHO by Monsanto International Services, Brussels).

Panshina TN (1973) [Materials about toxicology of new herbicide Ramrod.] Gig Primen toksikol pestic klin otravlenni, 1973: 301-303 (in Russian).

Panshina TN (1976) [Hygienic aspects of the use of certain herbicides in agriculture and toxicology.] Gig i Sanit, 7: 38-41 (in Russian).

Panshina TN (1977) Establishment of maximum permissible concentrations and approximately safe levels of action exerted by herbicides of haloid-substituted carboxylic acid anilides in the air of a production sector. Gig Tr Prof Zabol, 12: 30-33 (in Russian).

Panshina TN (1985) IRPTC scientific reviews of Soviet literature on toxicity and hazards of chemicals No. 83: Propachlor (Ramrod). Moscow, Centre of International Projects, GKNT, 19 pp.

Pantano LK & Anderson KS (1987) The metabolic fate of propachlor [2-chloro-N-(1-methylethyl)-N-Phenylacetamide] in sorghum foliage and grain (Project No. MSL-5412). St. Louis, Missouri, Monsanto Agricultural Company (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Pekas JV, Larsen GL, & Feil VJ (1979) Propachlor detoxication in the small intestine: cysteine conjugation. J Toxicol environ Health, 5: 653-662.

Pietrzik J (1991) [Laboratory determination of side effects of Ramrod 65WP on the short-winged beetle *Aleochara bilineata* Gyll (Project No. 112/01-AB).] Niefern-Ochselbronn, Austria, GAB Biotechnologie GmbH (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels) (in German).

Pilinskaya M, Kurinny AI, & Ivova TS (1980) [The primary evaluation of cytogenetic activity and potential mutagenic hazard of 22 pesticides.] Cytol Genet, 14(6): 41-46 (in Russian).

Plewa MJ, Wagner ED, Glenda G, & Gentille JM (1984) An evaluation of the genotoxic properties of herbicides following plant and animal activation. Mutat Res, **136**: 233-245.

Pressley TA & Longbottom JE (1982) The determination of organochlorine pesticides in industrial and municipal waste water. Cincinnati, Ohio, US Environmental Protection Agency, Environmental Monitoring and Support Laboratory, Office of Research and Development.

Rafter JJ, Bakke J, Larsen G, Gustafson B, & Gustafson JA (1983a) Role of the intestinal microflora in the formation of sulfur-containing conjugates of xenobiotics. Rev Biochem Toxicol, **5**: 387-408.

Rafter JJ, Gustafson JA, Bakke J, Larsen G, Norin KE, & Gustafson BE (1983b) Studies on the re-establishment of the intestinal microflora in germ-free rats with special reference to the metabolism of N-isopropyl-alpha-chloracetanilide (propachlor). Xenobiotica, **13**(3): 171-178.

Rankov V & Velev B (1976) Effect of temperature on the interaction between the metribuzin and propachlor herbicides and soil microorganisms. Agrokhimiya, **11**(5): 100-105.

Rankov V & Velev B (1977) Detoxication of the herbicide propachlor by certain microscopic fungi. Acta phytopathol Acad Sci Hung, **12**(1-2): 67-72.

Rao KS (1981) Two-generation dietary reproduction study with propachlor in rats (Study No. HET-K-077810(8)). Midland, Michigan, Dow Chemical Company, Health and Environmental Science, Toxicology Research Laboratory, 171 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Rejtö M, Saltzman S, & Acher AJ (1984) Photodecomposition of propachlor. J Agric Food Chem, **32**: 226-230.

Reyna MS & Ribelin WE (1984a) Three-month feeding study of propachlor to albino rats (Study No. 83037). Newstead, St. Louis, Monsanto Environmental Health Laboratory (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Reyna MS & Ribelin WE (1984b) Three-month feeding study of propachlor to albino mice (Study No. 820061). Newstead, St. Louis, Monsanto Environmental Health Laboratory (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Richards C & Kaiser FE (1984) Acute toxicity of propachlor (AB 83-367) to *Selenastrum capricornutum* Printz. Columbia, Missouri, Analytical Biochemistry Laboratories, 39 pp (Unpublished proprietary report No. 31348, submitted to WHO by Monsanto International Services, Brussels).

Ritter WP, Johnson HP, & Lovely WG (1973) Diffusion of atrazine, propachlor, and diazinon in silt loam soil. Weed Sci, **5**: 381-384.

Roberts HA, Walker A, & Bond W (1978) Persistence of chlorthaldimethyl activity in soil. In: Proceedings of the British Crop Protection Conference: Weeds. Croydon, British Crop Protection Council, pp 87-92.

Schardein JW (1982) Teratology study in rabbits. Mattawan, Michigan, International Research and Development Corporation, 47 pp (Unpublished proprietary report No. IR 81-224, submitted to WHO by Monsanto International Services, Brussels).

Schardein JW & Wahlberg A (1982) Teratology study in rats. Mattawan, Michigan, International Research and Development Corporation, 81 pp (Unpublished proprietary report No. IR 81-264, submitted to WHO by Monsanto International Services, Brussels).

Shirko ST & Belova VL (1982) [Level of Ramrod, semeron, and mesoranil in the soil and cabbage plants in relation of dose of nitrogen and potassium.] Khim Sel'skom Khoz, 20(1): 51-53 (in Russian).

Sjovall J, Rafter J, Larsen G, & Egestad B (1983) Lipophilic ion exchange for group separation of conjugated metabolites of xenobiotics. J Chromatogr, 276: 150-156.

Spalding RF & Snow DD (1989) Stream levels of agrochemicals during a spring discharge event. Chemosphere, 19(8/9): 1129-1140.

Steen WC & Collette TW (1989) Microbial degradation of seven amides by suspended bacterial populations. Appl Environ Microbiol, 55(10): 2545-2549.

Steinmetz L & Mirsalis C (1984) Evaluation of the potential of propachlor to induce unscheduled DNA synthesis in the primary rat hepatocyte cultures (Project No. LSC-7538). Menlo Park, California, Stanford Research Institute, 8 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Steinmetz L & Mirsalis C (1986) Evaluation of the potential of propachlor to induce unscheduled DNA synthesis in the *in vivo- in vitro* rat hepatocyte DNA repair assay (Project No. LSC-2021). Menlo Park, California, Stanford Research Institute, 37 pp (Unpublished proprietary report submitted to WHO by Monsanto International Services, Brussels).

Stereva M & Maleva E (1977) [Biochemical studies on changes in gonads of male white rats under combined action of low frequency vibrations and intoxication with Ramrod. II. Dynamic in changes of 5-nucleotidase activity.] In: [Proceedings of the National Scientific Session of Chemists with Medical Direction, Part I], pp 133-139 (in Bulgarian).

Strateva A (1974a) [Hygienic-toxicologic study on Ramrod aiming its hygienic standardization in water.] Sofia, University of Sofia (Dissertation) (in Bulgarian).

Strateva A (1974b) [Amid preparations with herbicide action. Experimental data on the acute oral toxicity of propachlor (Ramrod).] Exp Med Morphol, 13(2): 123-129 (in Russian).

Strateva A (1975) [On some toxicologic properties of Ramrod and their significance on its hygienic standardization in waters.] Hyg Zdraveopazvane, 18(4): 401-405 (in Russian).

Strateva A (1976) [The experimental determination of MAC of Ramrod in water.] Gig i Sanit, 4: 85-87 (in Russian).

Strateva A, Velisarov A, & Georgiev A (1974) [Morphological and enzymohistochemical investigations on some internal organs of experimental animals under the effect of Ramrod in acute experiment.] Hyg Zdraveopazvane, 17(3): 283-286 (in Russian).

Struble CB (1991) *In situ* intestinal absorption of 2-chloro-N-isopropylacetanilide (propachlor) and non-biliary excretion of metabolites into the intestinal tract of rats, pigs and chickens. Xenobiotica, **21**: 85-95.

Tanaka FS, Wien RG, & Mansager ER (1981) Survey for surfactant effects on the photodegradation of herbicides in aqueous media. J Agric Food Chem, **29**: 227-230.

Tanke W & Franz JM (1978) [Side effects of herbicides on economically useful insects.] Entomophaga, **23**(3): 275-280 (in German).

Thompson CM & Forbes AD (1979a) Acute toxicity of propachlor to *Daphnia magna*. Columbia, Missouri, ABC-Laboratories Inc., 40 pp (Unpublished proprietary report No. 24708, submitted to WHO by Monsanto International Services, Brussels).

Thompson CM & Forbes AD (1979b) Acute toxicity of propachlor to Rainbow trout *Salmo gairdneri*. Columbia, Missouri, ABC-Laboratories Inc., 40 pp (Unpublished proprietary report No. 24019, submitted to WHO by Monsanto International Services, Brussels).

Thun S (1990a) Propachlor 21-day reproduction test in *Daphnia* (Project Number XX-89-126). Walsrode, Germany, IBR Forschung GmbH (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Thun S (1990b) Prolonged fish toxicity test in the rainbow trout (*Salmo gairdneri*) (Project Number XX-89-163). Walsrode, Germany, IBR Forschung GmbH (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

Thun S, Lemke G, & Fulst S (1991) Acute toxicity in earthworms according to OECD 207. (Project Number IB-90-566). Walsrode, Germany, IBR Forschung GmbH (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

US EPA (1984a) Guidance for the registration of pesticide products containing propachlor (019101) (EPA Case number 17). Washington, DC, US Environmental Protection Agency, Office of Pesticide Programme.

US EPA (1984b) Health and environmental effects profile for propachlor. Cincinnati, Ohio, US Environmental Protection Agency (600/X-84/335).

US EPA (1988) Propachlor. Washington, DC, US Environmental Protection Agency, Health Advisory Office of Drinking-Water.

Vasilev NV (1982) [Residual quantity of Ramrod in soil and fodder rurabages.] Khim Sel'skom Khoz, **20**(6): 51-53 (in Russian).

Villarreal DT, Turco RF, & Konopka A (1991) Propachlor degradation by a soil bacterial community. Appl Environ Microbiol, **57**(8): 2135-2140.

Von Schubert H (1979) [Allergic contact dermatitis caused by propachlor.] Dermatol Monatsschr, **165**: 495-498 (in German).

Walker A & Brown PA (1982) Effects of soil on the activity and persistence of propachlor. In: Proceedings of the British Crop Protection Conference: Weeds. Croydon, British Crop Protection Council, pp 171-177.

Walker A & Brown PA (1985) The relative persistence in soil of five acetanilide herbicides. Bull Environ Contam Toxicol, **34**: 143-149.

Warholic DT, Gutenmann WH, & Lisk DJ (1983) Propachlor herbicide residue studies in cabbage using modified analytical procedure. Bull Environ Contam Toxicol, **31**: 585-587.

WHO/FAO (1989) Data sheets on pesticides No. 78: Propachlor. Geneva, World Health Organization, 7 pp (WHO/VBC/DS/87.78).

WHO (1990) The WHO recommended classification of pesticides by hazard and guidelines to classification 1990-91. Geneva, World Health Organization, 39 pp (WHO/PCS/90.1).

Worthing CR & Hance RJ (1991) The pesticide manual, 9th ed. Croydon, British Crop Protection Council.

Yu Ching Chien, Booth GM, Hansen DJ, & Larsen JR (1975) Fate of alachlor and propachlor in a model ecosystem. J Agric Food Chem, **23**(5): 877-878.

Zhukova PS & Shirko TS (1979) [Herbicide residues in soil and vegetables.] Khim Sel'skom Khoz, **17**(6): 46-50 (in Russian).

Zilkah S, Osband ME, & Mccaffrey RP (1981) Characterization of the inhibitory effects of the phytotoxic agent propachlor on L1210 cell proliferation. Cancer Lett. (Irel), **13**(3): 241-248.

Zilkah S, Osband ME, Mccaffrey RP, & Shapiro H (1985) The effect of the plant cell inhibitor propachlor on the cell cycle of LI210 cells as evaluated by flow cytometry. Life Sci, **6**: 2111-2115.

Zimdahl RL & Clark SK (1982) Degradation of three acetanilide herbicides in soil. Weed Sci, **30**: 545-548.

Zlateva M & Maleva E (1978) [Late changes in the gonads of male white rats upon combined treatment with low frequency vibrations and Ramrod intoxication.] Med Fizkult, pp 85-91 (in Bulgarian).

Zlateva M & Maleva E (1979) Disorders in the processes of division and differentiation of seminiferous epithelium in case of chronic intoxication with Ramrod. Exp Med Morphol, **18**(1): 35-39.

Zlateva M, Maleva E, & Stareva M (1978) Changes of adenosine triphosphatase activity in the testes of albino rats under combined influence of low-frequency vibration and intoxication with the herbicide Ramrod. Rev Toxicol Eur Res, **6**(78): 375-378.

Zschaler R & Jonas W (1990) Growth inhibition test with algae (Project No. NC-90-592). Hamburg, Natec Institut für Naturwissenschaftlich-technische Dienste GmbH. (Unpublished proprietary report of Monsanto Agricultural Company, submitted to WHO by Monsanto International Services, Brussels).

RESUME ET EVALUATION

1. Identité, modalités d'utilisation, propriétés physiques et chimiques, méthodes d'analyse

Le propachlor est un herbicide dérivé de l'acétanilide qu'on utilise depuis 1965 en traitement de pré-levée et en traitement précoce de post-levée. Il est principalement formulé en poudre mouillable, liquide (concentré en suspension) et granulés. On l'utilise en agriculture pour détruire les graminées annuelles et certaines adventices à feuilles larges dans des cultures comme le maïs, le sorgho, les potirons, le lin et les fleurs.

Le propachlor est légèrement soluble dans l'eau et facilement soluble dans la plupart des solvants organiques. Il est peu volatil, non inflammable et stable au rayonnement ultra-violet. La méthode d'analyse la plus pratique est la chromatographie en phase gazeuse avec détection par capture d'électrons après extraction et purification par des méthodes appropriées.

2. Transport, distribution et transformation dans l'environnement

Le propachlor ne semble pas subir de dégradation photochimique à la surface du sol. Il se volatilise en présence de vent lorsque la surface du sol est encore humide.

Il n'est que modérément adsorbé aux particules du sol et aux matières organiques, d'où un risque de lessivage à travers le sol jusqu'aux eaux souterraines. Toutefois toutes les études montrent que ce risque est faible en pratique. Il faut des précipitations très importantes pour que les résidus se déplacent de 30 cm à l'intérieur du sol. Selon la plupart des auteurs, la majorité des résidus demeurent à moins de 4 cm de profondeur. Les caractéristiques du sol influent beaucoup sur la mobilité du composé. Le lessivage se produit surtout dans des sols sableux pauvres en matières organiques.

On a étudié en laboratoire et sur le terrain l'entraînement du propachlor par ruissellement. Une des études a montré que la présence de matières organiques dans le sol réduisait de 7 à 1 % de la quantité appliquée, la concentration de l'herbicide dans l'eau de ruissellement. L'incorporation de propachlor dans le sol réduit

également les pertes par ruissellement (de 3 à 0,8 % selon une étude).

En ce qui concerne la réduction de la concentration de propachlor dans le sol et dans l'eau, le facteur de loin le plus important est sa dégradation par les micro-organismes. On a montré que bactéries et champignons étaient responsables de la dégradation de ce composé. Peu de bactéries sont apparemment capables d'utiliser le propachlor comme seule source de carbone. On a également isolé des bactéries qui sont en mesure d'utiliser des métabolites telluriques du propachlor.

Les principaux métabolites qui se forment dans le sol sont des acides oxaniliques et sulfoniques solubles dans l'eau. Il peut se former un grand nombre d'autres métabolites mais ils ne représentent qu'une faible proportion du total.

Le propachlor disparaît rapidement du sol et on a fait état de demi-vies allant jusqu'à trois semaines. La plupart des études indiquent une dégradation pratiquement complète en moins de six mois. Les conditions écologiques influent sur la vitesse de dégradation qui est favorisée par une température élevée et une forte humidité du sol. Les résultats qui indiquent une persistance élevée du propachlor dans le sol ont été obtenus à basse température et dans des sols secs. La présence de nutriments en quantité suffisante dans le sol est également nécessaire à la dégradation du propachlor.

Un des métabolites, la *N*-isopropylaniline conjuguée est beaucoup plus persistante que le composé initial. On a retrouvé des résidus de ce métabolite jusqu'à deux ans après l'épandage de propachlor à titre expérimental à des doses plus élevées que celles que l'on utilise normalement en agriculture.

Dans les conditions normales d'utilisation, le propachlor ne devrait pas être entraîné à travers le sol par lessivage jusqu'aux nappes souterraines et ne demeure pas dans le sol. Des conditions exceptionnelles (température très basse ou sécheresse) peuvent prolonger la persistance du propachlor et de ses métabolites.

Dans les conditions normales, le propachlor ne subit pas de dégradation photochimique importante dans l'eau. Cependant, en présence de photosensibilisateurs, cette dégradation photochimique peut se produire. Le propachlor est stable à

l'hydrolyse. Il est peu probable qu'il se volatilise à partir de l'eau du fait de sa forte solubilité dans l'eau et de sa faible tension de vapeur.

Comme dans le sol, c'est principalement par dégradation biologique que le propachlor s'élimine de l'eau. Sa vitesse d'élimination est donc liée à la population microbienne. Une étude effectuée sur de l'eau contenant peu de bactéries a permis d'obtenir une demi-vie d'environ cinq mois. Une autre étude a montré qu'au bout de six semaines, il n'y avait toujours pas d'ouverture du cycle. Des études de laboratoire portant sur des modèles d'écosystèmes ont montré que le propachlor était presque complètement dégradé en l'espace de 33 jours.

Plusieurs études portant sur différentes espèces végétales ont montré que le propachlor était rapidement métabolisé par les plantes intactes ainsi que par des tissus végétaux excisés. Les voies métaboliques se sont révélées analogues chez tous les végétaux étudiés, tout au moins pendant les six à 24 premières heures, conduisant à des métabolites hydrosolubles. On n'a pas observé de décomposition métabolique du reste *N*-isopropylaniline. Seule une très faible proportion (< 1 % selon une étude) des métabolites a été retrouvée dans les fruits de ces végétaux; ils étaient concentrés en grande majorité dans les racines et les feuilles. Les principaux métabolites produits par les plantes sont identiques à ceux qui prennent naissance dans le sol. On sait que ces métabolites peuvent être fixés à partir du sol et un certain nombre d'études ne permettent pas de déterminer avec certitude si les métabolites analysés proviennent de la plantes ou du sol.

Bien que, d'après le coefficient de partage octanol/eau, ce composé ait une tendance modérée à la bioaccumulation, on a montré qu'il n'y avait ni bioconcentration ni bioamplification chez les êtres vivants.

3. Concentrations dans l'environnement et exposition humaine

Les rapports d'analyse du propachlor dans l'air au cours de l'épandage sont rares et insuffisants.

Aux Etats-Unis d'Amérique, la concentration du propachlor dans les eaux de surface et les eaux souterraines est toujours faible, les maxima atteignant 10 μg/litre dans les eaux de surface

et 0,12 µg/litre dans les eaux souterraines. Le concentration la plus forte enregistrée lors d'une étude sur les eaux de ruissellement était de 46 µg/litre.

Les résidus de propachlor dans les denrées alimentaires sont généralement inférieurs à la limite de détection de la méthode d'analyse (0,005 mg/kg). L'expérimentation a permis de retrouver des résidus de l'ordre de 0,005 mg/kg dans des tomates, des poivrons, des oignons et des choux.

Le dosage du propachlor dans l'atmosphère de la zone de travail de conducteurs de tracteur pendant l'épandage du composé a donné des résultats allant de 0,1 à 3,7 mg/m^3.

4. Cinétique et métabolisme

Chez les mammifères, le propachlor peut être absorbé au niveau des voies respiratoires, des voies digestives et de la peau. Il ne s'accumule pas dans l'organisme et devient indétectable au bout de 48 heures.

La plupart des espèces animales (rats, porcs, poulets) métabolisent le propachlor par la voie de l'acide mercapturique (MAP). Il se forme des conjugués de cystéine par conjugaison avec le glutathion et on a avancé que ces conjugués jouaient le rôle d'intermédiaires dans la formation métabolique des acides mercapturiques. La métabolisation du conjugué cystéinique du propachlor se poursuit, notamment sous l'action de la C-S lyase bactérienne qui intervient également dans la formation des métabolites terminaux contenant le groupement méthylsulfonyle, métabolites qui sont principalement excrétés dans l'urine (68 % de la dose initiale de propachlor) et, sous forme de résidus insolubles, dans les matières fécales (19 %). La C-S lyase du propachlor est sans action chez les rats axéniques.

On a montré qu'il y avait un certain nombre de différences dans le métabolisme du propachlor chez le rat et le porc. La bile est la principale voie d'élimination des métabolites mercapturiques chez le rat, mais on a montré qu'il existait une voie métabolique extra-biliaire chez le porc.

Des études de métabolisme effectués sur des veaux ont montré que ces animaux pourraient être incapables de former de l'acide

mercapturique à partir des conjugués du glutathion, ce qui les rendrait plus sensibles à l'intoxication par le propachlor.

5. Effets sur les animaux d'expérience et les systèmes d'épreuves *in vitro*

Le propachlor est légèrement toxique en cas d'exposition aiguë par voie orale (la DL_{50} pour le rat varie de 950 à 2176 mg/kg de poids corporel). Les signes d'intoxication aiguë proviennent principalement d'effets sur le système nerveux central (excitation et convulsions suivies d'une dépression). Chez des rongeurs, la toxicité aiguë par inhalation est faible (CL_{50} = 1,0 mg/litre). Le propachlor provoque de graves irritations des yeux et de la peau.

Des rats, des souris et des chiens ont été soumis à une exposition de longue ou de courte durée au propachlor. Les organes cibles sont le foie et les reins. Chez le chien, la dose sans effet nocif observable a été de 45 mg/kg de poids corporel lors d'une étude de trois mois où l'animal était exposé par la voie alimentaire. Lors d'une étude d'une année sur des chiens, la dose sans effet nocif observable a été estimée à 9 mg/kg de poids corporel (200 ppm dans la nourriture). Lors d'une étude sur des rats exposés de la même manière pendant 24 mois au propachlor, la dose sans effet observable a été évaluée à 50 mg/kg de nourriture (2,6 mg/kg de poids corporel). Lors d'une étude semblable effectuée sur des souris pendant 18 mois, on a évalué à 1,6 mg/kg de poids corporel (10 ppm) la dose sans effet observable.

Le propachlor ne s'est révélé cancérogène ni pour la souris ni pour le rat. Dans la plupart des systèmes d'épreuve mammaliens, sa réponse mutagène est négative tout en étant positive dans quelques autres cas. Les données expérimentales disponibles de fournissent pas une preuve suffisante de son pouvoir mutagène.

Administré en dose unique (675 mg/kg) à des rats et à des souris, le propachlor a donné lieu à des signes d'embryotoxicité. On a également observé des effets embryotoxiques lors d'études où du propachlor avait été administré à plusieurs reprises (35,7 à 270 mg/kg). Toutefois, lors d'une autre étude sur des rats, où les doses variaient de 20 à 200 mg/kg, aucun effet embryotoxique n'a été observé.

Aux doses respectives de 12 et 60 mg/kg de poids corporel, le propachlor (en poudre mouillable) a entraîné une réduction de la teneur en protéines et un accroissement de l'activité de l'ATPase et de la 5-nucléotidase dans des homogénats de testicules de rats, provoquant également une dégénérescence du tissu testiculaire. Lors d'une étude de reproduction portant sur deux générations, on n'a pas véritablement obtenu la preuve d'effets indésirables.

6. Effets sur l'homme

On a signalé quelques dermatites de contact et dermatites allergiques chez des agriculteurs et des ouvriers de production exposés au propachlor (Ramrod et Satecid). Des tests cutanés ont été effectués parmi un certain nombre d'entre eux, avec un résultat positif, qui révèle une réaction d'irritation et une hypersensibilité mono- et bivalente.

On n'a pas eu connaissance de symptômes ou de maladies, soit chez des personnes exposées de par leur profession, soit dans la population générale - à part les quelques cas d'effets cutanés chez les ouvriers professionnellement exposés.

7. Effets sur les êtres vivant dans leur milieu naturel

Des études portant sur la microflore terricole ont montré que les bactéries nitrifiantes constituaient le groupe le plus sensible aux effets inhibiteurs du propachlor, leur nombre étant réduit d'un facteur 3 à 4 après épandage de 8 à 10 kg de propachlor par hectare. Ce sont les bactéries décomposant la cellulose qui étaient les moins sensibles. La forte adsorption du propachlor aux particules d'argile présentes dans le sol et une température élevée sont deux facteurs qui réduisent les effets inhibiteurs.

Chez l'algue *Selenastrum capricornutum*, on a fait état d'une CE_{50} à 96 heures de 0,02 mg/litre (pour la croissance) et d'une concentration sans effet observable de 0,01 mg/litre. D'après une deuxième étude portant sur une formulation de propachlor et menée pendant 72 heures, le risque pour cette même algue serait nettement moindre.

Pour la daphnie *Daphnia magna*, on donne des CL_{50} de 7,8 ou 6,9 mg/litre et une concentration sans effet observable inférieure à 5,6 mg/litre. La concentration sans effet observable sur la reproduction était de 0,097 mg/litre. Pour des larves de deux

espèces de moucherons, on a obtenu pour la CL_{50} des valeurs respectives de 0,79 et 1,8 mg/litre.

Chez la truite arc-en-ciel la CL_{50} à 96 heures est de 0,17 mg/litre et la concentration sans effet observable sur 21 jours, de 0,019 mg/litre.

Le propachlor est considéré comme modérément à fortement toxique pour les organismes aquatiques.

Le propachlor n'est pas toxique pour les lombrics aux concentrations présentes dans le sol par suite d'un usage normal (la concentration sans effet observable est de 100 mg/kg de terre). La DL_{50} par contact pour les abeilles (311 μg/abeille) montre que le propachlor ne constitue pas un danger pour ces insectes. En revanche, des études menées en laboratoire et sur le terrain montrent que des parasites utiles peuvent souffrir des effets du propachlor.

Le propachlor est plus toxique pour les oiseaux lorsqu'on l'introduit directement dans l'estomac que lorsqu'on l'administre dans la nourriture. La DL_{50} aiguë varie de 137 à 735 mg/kg de poids corporel pour différentes espèces. Quant à la CL_{50} lors d'une exposition par voie alimentaire, elle dépasse 5620 mg/kg de nourriture chez les oiseaux.

Le propachlor ne constitue pas un danger pour les oiseaux dans la nature, même sous forme de granulés.

RESUMEN Y EVALUACION

1. Identidad, modalidades de uso, propiedades físicas y químicas y métodos analíticos

El propacloro es un herbicida derivado de la acetanilida utilizado desde 1965 que actúa en las plantas antes de nacer o poco después. Las principales formulaciones son de polvo humectable, líquido fluido (concentrado en suspensión) y gránulos. Se aplica en la agricultura a la lucha contra las gramíneas anuales y algunas malas hierbas de hoja ancha en varios cultivos, como los de maíz, sorgo, calabaza, lino y flores ornamentales.

El propacloro es ligeramente soluble en agua y se disuelve fácilmente en la mayoría de los disolventes orgánicos. Su volatilidad es escasa, no es inflamable y es estable a la radiación ultravioleta. El método más práctico de análisis es la cromatografía de gases con detección por captura de electrones, después de aplicar procedimientos apropiados de extracción y purificación.

2. Transporte, distribución y transformación en el medio ambiente

Según la información disponible, el propacloro no se fotodegrada sobre la superficie del suelo. El producto se volatiliza cuando hay viento y la superficie del suelo está todavía mojada.

La adsorción sobre las partículas del suelo y la materia orgánica es sólo moderada. Debido a esto, es posible la lixiviación a través del perfil del suelo hacia el agua subterránea. Sin embargo, todos los estudios indican que en la práctica es poco probable que esto ocurra. Se requiere una precipitación muy abundante para hacer descender los residuos 30 cm en el perfil del suelo. La mayoría de los autores señalan que la mayor parte de los residuos se mantienen en una capa superficial del suelo de 4 cm. Las características del suelo influyen mucho en el desplazamiento del producto. La lixiviación se produce en su mayor parte en suelo arenoso con poca materia orgánica.

Se ha estudiado el arrastre del propacloro por el agua tanto en el laboratorio como sobre el terreno. En un estudio, la materia orgánica del suelo redujo el arrastre del herbicida aplicado del 7%

al 1%. Su incorporación al suelo también redujo la pérdida por arrastre del agua (del 3% al 0,8% en un estudio).

El factor que más contribuye, con diferencia, a reducir los niveles de propacloro en el suelo y el agua es la degradación por los microorganismos. Se ha comprobado que en la degradación de la sustancia intervienen tanto bacterias como hongos. Son pocas las bacterias que parecen tener capacidad para usar el propacloro como única fuente de carbono. También se han aislado bacterias que pueden utilizar los metabolitos del propacloro presentes en el suelo.

Los metabolitos predominantes entre los que se forman en el suelo son los ácidos oxanílico y sulfónico, solubles en agua. Pueden formarse otros muchos metabolitos, pero representan una proporción pequeña del total.

El propacloro desaparece con rapidez del suelo, habiéndose registrado semividas de hasta tres semanas. En la mayoría de los estudios se señala que la degradación es casi completa en menos de seis meses. Las condiciones del medio ambiente influyen en la velocidad de degradación, que se ve favorecida por los valores elevados de la temperatura y el contenido de humedad del suelo. Los estudios en los que se describía una permanencia más prolongada del propacloro en el suelo se realizaron en condiciones de baja temperatura o suelo seco. También es necesaria una cantidad suficiente de nutrientes en el suelo para la degradación.

El metabolito conjugado *N*-isopropilanilina es mucho más persistente que el producto del que procede. Se han encontrado residuos de este metabolito hasta dos años después de la aplicación experimental de dosis de propacloro más altas de las que se utilizan normalmente en la agricultura.

Con el uso normal no es previsible que el propacloro llegue por lixiviación a través del suelo hasta el agua subterránea, y no se mantiene mucho tiempo en el suelo. En condiciones excepcionales de baja temperatura o sequedad, el propacloro y sus metabolitos pueden permanecer más tiempo en él. En condiciones normales, el propacloro no sufre una fotodegradación significativa en el agua. En presencia de fotosensibilizadores puede fotodegradarse. El propacloro es estable desde el punto de vista hidrolítico. No es probable la volatilización a partir del agua, debido a la elevada solubilidad en ella y la baja tensión de vapor del producto.

Al igual que en el suelo, la principal ruta de pérdida de propacloro del agua es la degradación biótica. La velocidad de desaparición del propacloro del agua depende, pues, de la población microbiana. En un estudio realizado con un pequeño número de bacterias presentes en el agua se obtuvo una semivida de unos cinco meses. En otro estudio, a las seis semanas no se había roto el anillo. En estudios de laboratorio con modelos de ecosistemas se observó una degradación casi completa en un período de 33 días.

En varios estudios con distintas especies vegetales se vio que el propacloro se metabolizaba con rapidez tanto en las plantas intactas como en tejidos vegetales extirpados. Las rutas metabólicas eran análogas en todas las plantas estudiadas, por lo menos durante las primeras 6-24 horas, produciendo metabolitos hidrosolubles. No se observó degradación metabólica del fragmento de la *N*-isopropilanilina. En los frutos de las plantas solamente se encontró una proporción muy pequeña (< 1% en un estudio) de los metabolitos; en su mayor parte estaban en las raíces y el follaje. Los principales metabolitos producidos en las plantas son idénticos a los que se forman en el suelo. Se sabe que las plantas absorben esos metabolitos del suelo, y en algunos estudios había dudas acerca de si los metabolitos medidos procedían de la planta o del suelo.

Aunque del coeficiente de reparto en octanol y agua parece deducirse un potencial moderado de bioacumulación, los estudios realizados indican que no hay ni bioconcentración ni bioamplificación en los organismos.

3. Niveles medioambientales y exposición humana

Las mediciones descritas de la concentración del propacloro en el aire durante la aplicación son pocas e inadecuadas.

Las concentraciones en el agua superficial y subterránea en los Estados Unidos fueron siempre bajas, con un máximo de 10 µg/litro en la superficial y de 0,12 µg/litro en la subterránea. La mayor concentración registrada en el agua en un estudio del arrastre fue de 46 µg/litro.

Los residuos de propacloro en los alimentos suelen ser inferiores al límite de detección del método analítico (0,005 mg/kg). En estudios experimentales se han identificado

concentraciones de residuos del orden de 0,05 mg/kg en tomates, pimientos, cebollas y coles.

Las concentraciones de propacloro en el aire de la zona de trabajo de los conductores de tractores que aplicaban la sustancia oscilaban entre 0,1 y 3,7 mg/m^3.

4. Cinética y metabolismo

Los mamíferos pueden absorber el propacloro por los tractos respiratorio y gastrointestinal, así como a través de la piel. El producto no se acumula en el organismo, en el que no es detectable a las 48 horas.

La mayoría de las especies animales (ratas, cerdos, pollos) metabolizan el propacloro siguiendo la vía de los ácidos mercaptúricos. Mediante conjugación con el glutatión se forman productos conjugados de cisteína, que se han señalado como posibles intermediarios en la formación metabólica de ácidos mercaptúricos. La C-S liasa bacteriana participa en el ulterior metabolismo del sistema conjugado del propacloro con la cisteína y en la formación de los metabolitos finales con metilsulfonilo, que se excretan sobre todo en la orina (68% de la dosis de propacloro), y de residuos insolubles, que se excretan en las heces (19%). La propacloro C-S liasa es inactiva en ratas sin microorganismos.

En los estudios realizados se observaron algunas diferencias en cuanto al metabolismo entre las ratas y los cerdos. La bilis es el principal camino de eliminación de los metabolitos de la vía de los ácidos mercaptúricos en las ratas, pero se ha demostrado que en los cerdos existe una vía metabólica extrabiliar.

En estudios metabólicos con terneros se observó que pueden ser incapaces de formar ácidos mercaptúricos a partir de los productos conjugados del glutatión, por lo que pueden ser más susceptibles a la intoxicación.

5. Efectos en los animales de experimentación y en sistemas de prueba *in vitro*

El propacloro es ligeramente tóxico en la exposición oral aguda (la DL_{50} en ratas va de 950 a 2176 mg/kg de peso corporal). Los signos de intoxicación aguda son predominantemente efectos sobre el sistema nervioso central (excitación y convulsiones, seguidas de

depresión). La toxicidad aguda por inhalación en roedores es baja (CL_{50} = 1,0 mg/litro). El propacloro produjo efectos graves de irritación en los ojos y la piel.

El propacloro se ha ensayado en estudios de exposición de corta y larga duración en ratas, ratones y perros. Los órganos sobre los que actuaba eran el hígado y los riñones. En un estudio de administración con los alimentos a perros durante tres meses, el nivel sin efectos adversos observados (NOAEL) fue de 45 mg/kg de peso corporal. En otro estudio de un año, también en perros, el NOAEL fue de 9 mg/kg de peso corporal (250 ppm en la dieta). El nivel sin efectos observados (NOEL) en un estudio de alimentación de ratas durante 24 meses fue de 50 mg/kg de la dieta (2,6 mg/kg de peso corporal). En un estudio en el que administró el producto a ratones con los alimentos durante 18 meses, el NOEL fue de 1,6 mg/kg de peso corporal (10 ppm).

No se encontraron efectos carcinogénicos del propacloro en ratones y ratas. En la mayoría de los sistemas de prueba de mamíferos la respuesta mutagénica fue negativa, obteniéndose resultados positivos en un pequeño número de ensayos. Los datos experimentales disponibles no aportan suficientes pruebas de su potencial mutagénico.

En pruebas de dosis única (675 mg/kg) con ratones y ratas se demostró la embriotoxicidad del propacloro. También se detectaron efectos embriotóxicos en tratamientos con dosis repetidas (35,7-270 mg/kg). Sin embargo, en otro estudio en ratas, con una gama de dosis de 20-200 mg/kg, no se observó embriotoxicidad.

Con niveles de 12 y 60 mg/kg de peso corporal, el propacloro (polvo humectable) provocó una disminución del contenido de proteínas y un aumento de la actividad de la ATPasa y la 5-nucleotidasa en un homogeneizado de testículo de rata y cambios degenerativos en los testículos. En un estudio de reproducción de dos generaciones no se obtuvieron pruebas definitivas de efectos adversos.

6. Efectos en la especie humana

Se ha descrito un pequeño número de casos de dermatitis de contacto y alérgica en agricultores y trabajadores expuestos al propacloro durante la producción (Ramrod y Satecid). En algunos

de ellos se efectuaron pruebas del parche y la reacción fue positiva, con irritación e hipersensibilidad monovalente y bivalente.

No se han notificado casos de síntomas o enfermedades entre las personas expuestas profesionalmente o en la población general, salvo un pequeño número de informes de sus efectos cutáneos en trabajadores expuestos profesionalmente.

7. Efectos en los seres vivos del medio ambiente

En varios estudios sobre los microorganismos del suelo, las bacterias nitrificantes fueron el grupo mas sensible a los efectos inhibidores del propacloro, reduciéndose su número a la tercera o cuarta parte tras la aplicación de 8-10 kg/ha de propacloro. Las menos sensibles fueron las bacterias celulolíticas. La adsorción elevada sobre las partículas de arcilla del suelo y la temperatura alta reducen los efectos inhibidores.

En el alga *Selenastrum capricornutum* se ha registrado una CE_{50} a las 96 horas de 0,02 mg/litro para el crecimiento y una concentración sin efectos observados (NOEC) de 0,01 mg/litro. De un segundo estudio de 72 horas realizado con una formulación, parece desprenderse que el peligro es mucho menor para este mismo organismo.

Se ha informado de unos valores de la CL_{50} para *Daphnia magna* de 7,8 y 6,9 mg/litro y una NOEC de < 5,6 mg/litro. En las larvas de dos especies de moscas enanas, los valores registrados de la CL_{50} fueron de 0,79 y 1,8 mg/litro.

La CL_{50} para la trucha arcoiris a las 96 horas es de 0,17 mg/litro, y la NOEC en un estudio de 26 días fue de 0,019 mg/litro.

Se considera que el propacloro tiene una toxicidad entre moderada e intensa para los organismos acuáticos.

La exposición a las concentraciones de propacloro que cabe prever en el suelo no es tóxica para las lombrices de tierra si la aplicación es normal (la NOEC es de 100 mg/kg de suelo). La DL_{50} por contacto para las abejas (311 μg/abeja) demuestra que el propacloro no representa un peligro para estos insectos. En estudios de laboratorio y de campo se han detectado efectos

adversos del propacloro en algunos insectos parasitarios beneficiosos.

El propacloro es más tóxico para las aves cuando se administra mediante sonda gástrica que cuando se incorpora a la dieta. Los valores de la DL_{50} aguda para distintas especies de aves oscilan entre 137 y 735 mg/kg de peso corporal. Los valores de la CL_{50} en la administración con los alimentos fueron superiores a los 5620 mg/kg de la dieta.

El propacloro no representa un peligro para las aves en el campo, ni siquiera con la formulación granulada.

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