IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

UNEP

Environmental Health Criteria 198

Diazinon

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO and OECD

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continued at end of book

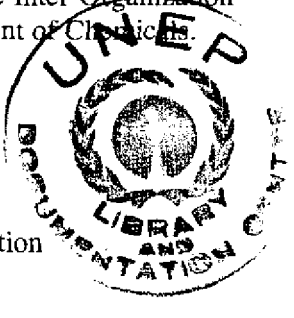
This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization.

Environmental Health Criteria 198

DIAZINON

First draft prepared by Dr K. Barabás, Albert Szent-Gyorgyi University Medical School, Szeged, Hungary

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



World Health Organization
Geneva, 1998

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer-review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR DIAZINON

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 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, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 - 9799111, fax no. + 41 22 - 7973460, E-mail irptc@unep.ch).

* * *

Financial support for this Task Group meeting was provided by the United Kingdom Department of Health as part of its contributions to the IPCS.

Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully

recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of

risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary - a review of the salient facts and the risk evaluation of the chemical
- Identity - physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment;

international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

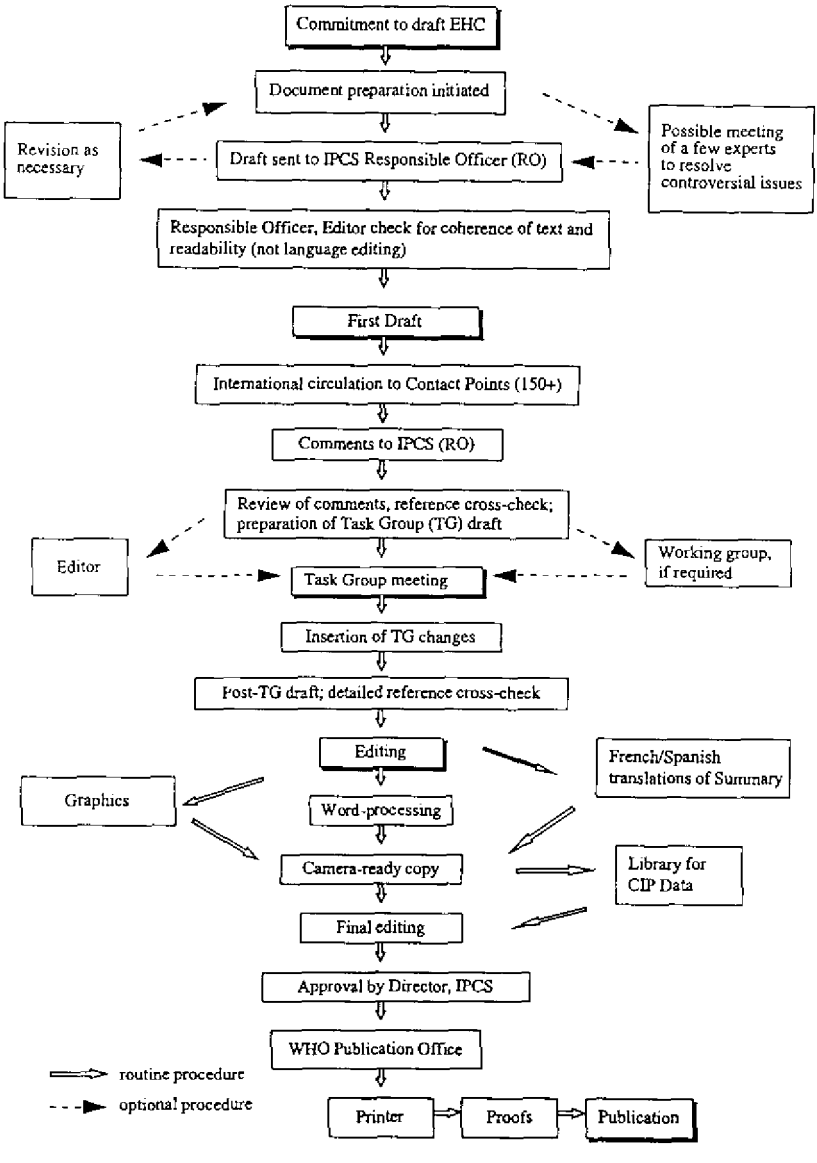
Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and

EHC PREPARATION FLOW CHART



recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR DIAZINON

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ENVIRONMENTAL HEALTH CRITERIA FOR DIAZINON

The Core Assessment Group (CAG) of the Joint Meeting on Pesticides (JMP) met at the Institute for Environment and Health, Leicester, United Kingdom, from 3 to 8 March 1997. Dr L.L. Smith welcomed the participants on behalf of the Institute and Dr R. Plestina on behalf of the three IPCS cooperating organizations (UNEP/ILO/WHO). The CAG reviewed and revised the draft monograph and made an evaluation of the risks for human health and the environment from exposure to diazinon.

The first draft of the monograph was prepared by Dr K. Barabás, Albert Szent-Gyorgyi University Medical School, Szeged, Hungary. Extensive scientific comments were received following circulation of the first draft to the IPCS contact points for Environmental Health Criteria monographs and these comments were incorporated into the second draft by the Secretariat.

Dr R. Plestina and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the overall scientific content and technical editing, respectively.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

ABBREVIATIONS

AChE	acetylcholinesterase
ai	active ingredient
ChE	cholinesterase
CNS	central nervous system
DETP	diethylthiophosphate
DT	degradation time
EDTA	ethylenediaminetetraacetic acid
fc	field capacity
GABA	gamma-aminobutyric acid
ip	intraperitoneal
MRL	maximum residue limit
NAD	nicotinamide adenine dinucleotide
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
OSHA	Occupational Safety and Health Administration (USA)
2-PAM	pralidoxine (2-pyridine aldoxime methyl) chloride
PEC	predicted environmental concentration
TEPP	tetraethyl-pyrophosphate
TER	toxicity-exposure ratio
TLV	threshold limit value

1. SUMMARY

1.1 Identity, physical and chemical properties, analytical methods

The chemical name for diazinon is *O,O*-diethyl *O*-2-isopropyl-6-methylpyrimidinyl-4-yl phosphorothioate. The pure material forms a colourless liquid with a faint ester-like odour. The technical active ingredient is a yellow/brown liquid with a slight compound-specific odour. The boiling point is 83-84 °C at 26.6 mPa and the vapour pressure (volatility) is low (9.7 mPa at 20 °C). The solubility in water at room temperature is 60 mg/litre. Diazinon is soluble in most organic solvents and has an octanol/water partition coefficient (log P_{ow}) of 3.40. It is stable in neutral media, but is slowly hydrolysed in alkaline media and more rapidly in acid media. It decomposes at temperatures above 120 °C.

A large number of sampling and analytical methods have been developed for the determination of diazinon and its metabolites in different media. Sensitive methods, such as gas chromatography, high-performance liquid chromatography, mass spectrometry and immunoassay methods, are increasingly used.

1.2 Production, uses and sources of human and environmental exposure

Diazinon is a contact organophosphorus insecticide with a wide range of insecticidal activity. It is effective against adult and juvenile forms of flying insects, crawling insects, acarians and spiders. It has been used from the early 1950s. Diazinon is mainly formulated as wettable powders and emulsifiable concentrates. It is also available in mixed formulations with other insecticides.

1.3 Environmental transport, distribution and transformation

Volatilization of diazinon from soil is of minor importance. Diazinon has a tropospheric half-life of 1.5 h.

The movement of diazinon through soil is highly influenced by a number of factors, particularly by organic matter and calcium carbonate content. Diazinon is not expected to bind strongly to soil,

owing to its K_{OC} value of 500, and is expected to show moderate mobility in the soil.

Biological processes appear to be the main factor in the degradation of diazinon in soil. At 20 °C and a soil moisture content of 60% of field capacity (f.c.) in a silt loam soil, the DT_{50} was 5 days. Under sterile conditions at 20 °C and 60% f.c., the DT_{50} was 118 days, suggesting that biological activity is mainly responsible for degradation in soil.

In natural water diazinon has a half-life of the order of 5-15 days. Both chemical and biological processes seem to play a role in the degradation of diazinon, leading to mineralization within a few weeks.

Uptake of diazinon by aquatic organisms is rapid. Low bioconcentration factors have been reported for aquatic organisms, ranging from 3 for shrimp to 152 for gudgeon, consistent with rapid metabolism and loss. Depuration half-lives for fish have been reported to be up to 30 h (muscle).

1.4 Environmental levels and human exposure

Environmental levels of diazinon are generally low. The routes of exposure for the general population are inhalational and dietary. Exposure through water is negligible. Occupational exposure is primarily dermal.

Diazinon uses fall into two major categories: as a pesticide in agriculture and as a drug in veterinary medicine. Thus, the major source of diazinon residues in edible crops are from its use as an agricultural pesticide, while those in meat, offal and other animal products arise from its use as a veterinary drug containing active ingredient.

Diazinon residues in vegetables, fruits and animal products are very low. The results of total-diet studies suggest that diazinon rapidly breaks down in both plant and animal products. Diazinon has not been detected in drinking-water samples and its concentrations in surface water are at the level of ng/litre.

1.5 Kinetics and metabolism

Diazinon may be absorbed from the gastrointestinal tract, through the intact skin and following inhalation. Transdermal absorption in humans is low. Diazinon is oxidized by the microsomal enzymes to cholinesterase-inhibiting metabolites such as diazoxon, hydroxydiazoxon, and hydroxydiazinon. Only minimal quantities of metabolites are detectable in milk and eggs. Diazinon and its metabolites do not accumulate in body tissue; 59-95% of an oral dose of diazinon is excreted within 24 h and 95-98% is excreted within 7 days, mainly in urine.

The main metabolic pathways of degradation of diazinon are:

a) Cleavage of the ester bond leading to the hydroxypyrimidine derivatives.

b) Transformation of P-S moiety to the P-O derivate.

c) Oxidation of isopropyl substituent leading to the corresponding tertiary and primary alcohol derivatives.

d) Oxidation of the methyl substituent leading to the corresponding alcohol.

e) Glutathione-mediated cleavage of the ester bond leading to a glutathione conjugate.

The cleavage of the phosphorus ester bond, leading directly, or via diazoxon, to the pyrimidyl metabolite plays the major role in the metabolism of diazinon. Metabolites maintaining the phosphorus ester bond are of transient nature and have been observed only in small quantities. Yields and rates of production of metabolites vary greatly between species. The production of diazoxon is not generally correlated with susceptibility to diazinon poisoning, although it is lowest in the least susceptible species, the sheep. The extrahepatic metabolism of diazinon, especially the hydrolysis of diazoxon in plasma, is more important toxicologically than the metabolism in the liver, although the liver is probably the most important site of metabolism in avian species. The metabolites formed, i.e. diethylphosphoric acid, diethylthiophosphoric acid and the derivates of the pyrimidinyl ring, are eliminated mainly via the kidneys.

1.6 Effects on experimental animals and *in vitro* test systems

Improvements in the manufacture of diazinon since 1979 have significantly reduced the content of highly toxic impurities, e.g., tetraethyl-pyrophosphate (TEPP). As a result of these progressive improvements, the acute oral LD_{50} of technical grade diazinon has increased (e.g., from 250 mg/kg to 1250 mg/kg in the rat).

The acute oral, dermal and inhalational toxicity is low. Short-term and long-term studies in mice, rats, rabbits, dogs and monkeys have shown that the only effect of concern is dose-related inhibition of acetyl cholinesterase activity.

Diazinon is slightly irritant to rabbit skin but not to the eye. Diazinon is not a dermal sensitizer. Reproductive and developmental studies have revealed no evidence of embryotoxic or teratogenic potential. There was no effect on reproductive performance at dose levels that were not toxic to the parent animals. Mutagenicity studies with various end-points *in vivo* and *in vitro* gave no evidence of a mutagenic potential. There is no evidence of carcinogenicity in rats or mice. Diazinon does not cause delayed neuropathy in hens. In the dog and guinea-pig, diazinon has been reported to cause acute pancreatitis; this is considered to be a species-specific effect.

1.7 Effects on humans

Several cases of accidental or suicidal poisoning by diazinon have been reported, some of which were fatal. In some of these the cholinergic syndrome may have been more severe than expected because of the presence of highly toxic impurities such as TEPP. In certain cases, acute reversible pancreatitis was associated with a severe cholinergic syndrome. This occurs also after poisoning with other cholinesterase inhibitors. In a number of cases, the intermediate syndrome was also observed. No cases of delayed neuropathy have ever been reported, as expected from animal data. Reported cases of poisoning after occupational exposure have always been associated with the presence of impurities such as TEPP, monothio-TEPP or sulfo-TEPP in the formulation. These impurities are unlikely to be found in currently available formulations.

1.8 Effects on other organisms in the laboratory and field

Effects of diazinon on unicellular algae are variable; both inhibition and stimulation of growth have been reported for different species at concentrations between 0.01 and 5 mg/litre. Generally, growth rates are reduced at concentration above 10 mg/litre, although in certain cases population size can remain unaltered at 100 mg/litre. Fewer and variable data make effects on other microorganisms difficult to assess.

Acute LC_{50} values for aquatic invertebrates range from 0.2 mg/litre for *Gammarus fasciatus* to 4.0 mg/litre for the shrimp *Hyallela azteca* in 96-h tests. Molluscs are substantially less sensitive according to a single test on the snail *Gillia attilis*. Sublethal effects on behaviour have been reported at concentrations between 0.1 and 0.01 mg/litre.

Acute LC_{50} values for fish range from 0.09 mg/litre for rainbow trout (*Oncorhynchus mykiss*) to 3.1 mg/litre for the catfish (*Channa punctatus*). Growth of early life stages of fish was inhibited at concentrations between 0.01 and 0.2 mg/litre. Brain acetylcholinesterase activity is suppressed following acute exposure to diazinon.

The LC_{50} for the earthworm *Eisenia foetida* in soil is 130 mg/kg soil.

The acute oral toxicity (LD_{50}) in birds ranges from 1.1 mg/kg body weight for Japanese quail to 85 mg/kg body weight for cowbirds. Dietary LC_{50} values range from 32 mg/kg diet for mallard to 900 mg/kg diet for Japanese quail (repellency was noted at these high dietary concentrations). The no-observed-effect concentration in diet for reproductive effects on birds in laboratory studies was 20 mg/kg diet for mallard and 40 mg/kg diet for bobwhite quail. Brain acetylcholinesterase activity is inhibited following ingestion. Diazinon may also be taken in via the dermal route. There have been reports of substantial field kills of water fowl following application of diazinon to turf. Field studies applying liquid formulations to turf at 4.8 kg ai/ha resulted in no mortality or reproductive effects on song birds. Application of granules caused a small reduction in song bird population size compared to that of controls. Ingestion of small numbers of granules can be fatal for small birds, as demonstrated in laboratory studies.

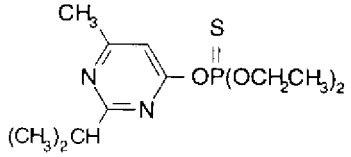
2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

2.1.1 Primary constituent

Common name: diazinon

Chemical structure:



Chemical formula: $C_{12}H_{21}N_2O_3PS$

Relative molecular mass: 304.35

IUPAC Chemical names: *O,O*-diethyl *O*-2-isopropyl-6-methyl-pyrimidin-4-yl phosphorothioate

CAS chemical name: *O,O*-diethyl *O*-[6-methyl-2-(1-methylethyl)-4-pirimidinyl] phosphorothioate

CAS registry number: 333-41-5

RTECS number: TF3325000

Official number: OMS 469; ENT 19 507

Synonyms: dimpylate, diazide, G.24480, Basudin, Kayazinon, Necidol/Nucidol

2.1.2 Technical product

Trade names: Diazinon (Alpha, Darlingtons Mushroom Laboratories, Murphy Chemicals and Rentokil); Basudin

(Ciba-Geigy); Crompest (Cromessel Co. Ltd); Dethlac (Gerhardt Pharmaceuticals); Isectalac (Sorex Ltd); Murphy Root Guard (Fisons); Rentokil Flytrol and Knox out 2FM (Rentokil); Secto AntSpray and Root Powder (Secto Ltd); Dazzel, Diagran, Dianon (Nippon Kayaku); Diazotol Gardentox, Nipsan (Nippon Kayaku); Dyzol, Dizion (Nippon Kayaku); Spectracide (Ciba-Geigy)

2.2 Physical and chemical properties

Diazinon is a clear colourless liquid (technical 95% yellow oil) with a faint ester-like odour.

Boiling point:	83-84 °C at 26.6 mPa; 125 °C at 133 mPa
Vapour pressure:	9.7 mPa at 20 °C
Density:	1.11 g/cm^3 at 20 °C
Refractive index:	1.4978-1.4981
Specific gravity:	1.116-1.118 at 20 °C
Stability:	susceptible to oxidation above 100 °C; stable in neutral media, but slowly hydrolysed in alkaline media, and more rapidly in acidic media
Decomposes:	above 120 °C
Corrosiveness:	non-corrosive
Solubility:	60 mg/litre in water at 20 °C; completely miscible with common organic solvents, e.g., ethers, acetone, alcohols, benzene, toluene, cyclohexane, hexane, dichloromethane, petroleum oils

2.3 Analytical methods

Formulated diazinon products are cleaned up by column chromatography to remove the basic impurities and analysed by titration with perchloric acid in acetic acid. They are also analysed by gas-liquid chromatography (Eberle et al., 1974; Allender & Britt, 1994).

Residues in soil, water, air, plants, foods, and animal and human tissues can be determined using gas chromatography using detectors selective for phosphorus-containing compounds, and by other chromatographic techniques. Table 1 outlines various methods for determination of diazinon in different media.

Farran et al. (1988a) described a method for the determination of organophosphorus insecticides and their hydrolysis products. The method involves the analysis of compounds by liquid chromatography in combination with UV and thermospray-mass spectrometric detection.

An automated identification method has been developed for water-borne toxicants, including diazinon, using an ion chromatography/high-performance liquid chromatography system (Fort et al., 1995).

A compendium of analytical methods for organophosphorus compounds has been issued (NIOSH, 1994).

Table 1. Analytical methods for diazinon

Medium	Analytical method	References
Air	adsorption on XAD-2 resin, gas chromatography with flame photometric detector	NIOSH (1994)
Soil	gas chromatography	Singmaster & Acin-Diaz (1991)
Water	extraction with XAD-2 resin, gas chromatography with nitrogen-phosphorus detector, gas chromatography/mass spectrometry	Le Bel et al. (1979)
	continuous-flow extraction coupled on-line with high-performance liquid chromatography	Farran et al. (1988b)
	liquid-solid extraction, gas chromatography/mass spectrometry	Johnson et al. (1991)
	on-line solid-phase extraction, liquid chromatography/thermal spray - mass spectrometry	Lacorte & Barcelo (1995)
	on-line solid-phase extraction, liquid chromatography/atmospheric pressure chemical ionization mass spectrometry	Lacorte & Barcelo (1996)
	maleic anhydride immunoassay	Winnett (1992)
Oil solution	gas chromatography	Koibuchi et al. (1975)
Fruit and vegetables	solvent extraction, gas chromatography with thermionic detector	Ferreira & Silva Fernandes (1980)
Apples	solvent extraction, gas chromatography with thermionic detector	Asensio et al. (1991)
Oranges	matrix solid-phase dispersion extraction, gas chromatography with electron capture detector	Torres et al. (1996)

Table 1 (contd).

Medium	Analytical method	References
Rice	solvent extraction, gas chromatography with flame ionization detector	Adachi et al. (1984)
Spinach	preparative thin-layer chromatography, autoradiography, liquid scintillation counting	Gilmore & Cortes (1966)
	solvent extraction, gas chromatography with electrolytic conductivity detector, gas chromatography/chemical ionization mass spectrometry	Cairns et al. (1985)
Milk	gas chromatography	Toyoda et al. (1990)
Human tissue	solvent extraction, thin-layer chromatography, gas chromatography with nitrogen-phosphorus detector	Kirkbride (1987)
Blood plasma	gas chromatography	Machin et al. (1975)
	solvent extraction, gas chromatography with electron capture detector	Wu et al. (1994)
Metabolites in urine		
DEP, DEPT	extraction by anion exchange resin, gas chromatography with flame photometric detector	Lores & Bradway (1977) Weisskcp & Seiber (1989)
GW7 550, GS 31 144	solvent extraction, gas chromatography with electrolytic conductivity detector	Lawrence & Iverson (1975)

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

Diazinon does not occur as a natural product.

3.2 Man-made sources

3.2.1 Production levels and processes

3.2.1.1 Manufacturing process

Diazinon is the common name for *O,O*-diethyl *O*-2-isopropyl-6-methylpyrimidin-4-yl phosphorothioate (IUPAC name), an organophosphate insecticide. Its insecticidal properties were first described by Gasser (1953) and it was introduced in 1952, by J. R. Geigy S.A. under the code number G 24480, trade names Basudin, Diazitol, Neocidol and Nucidol, and the protection of BP 713278; USP 2754243. Meanwhile, improvements in the manufacturing process and the stabilization of the technical grade diazinon by epoxidized soybean oil have significantly reduced the content and formation of toxic by-products and breakdown products and have reduced the acute toxicity of diazinon products.

3.2.2 Uses

Diazinon is a contact organophosphorus insecticide with a wide range of insecticidal activity, having long persistence and relatively low mammalian toxicity. Diazinon is effective against adult and juvenile forms of insects, but also against acarina. The spectrum of activity includes the following arthropod groups:

- flying insects: flies and fly maggots, mosquitoes
- crawling insects: cockroaches, bedbugs, lice and ants
- acarina: dog ticks
- arachnideae: spiders

The main applications are rice, fruit, vineyards, sugar-cane, corn, tobacco, potatoes, horticultural crops, animal dips and sprays.

Diazinon is also used by trained pest control operators in households and outbuildings to control cockroaches, ants, silverfish, spiders, carpet beetles and scorpions and in insecticidal collars on domestic pets.

3.2.3 Formulations

The most important diazinon formulations are: ULV concentrates, wettable powders 400 g/kg; emulsifiable concentrates 600, 400 and 250 g/litre; dust 20-40 g/kg; granules 30-140 g/kg; aerosols 200 g/litre.

Some typical formulations for agricultural and horticultural use include: Basudin 5 (50 g a.i./kg); Basudin 10 (100 g a.i./kg) GR; Basudin 40WP (400 g a.i./kg); Basudin 50SD (500 g a.i./kg); Basudin 60EC (EC 600 g a.i./litre); Diazitol Liquid; Basudin Ulvair 500; Basudin 20 Mushroom Aerosol, KN; Knox-out (Pennwalt), flowable microcapsules (230 g a.i./litre); Neocidol 60, Nucidol 60, EC (600 g a.i./litre) for veterinary use.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

4.1.1 Volatilization

It has been shown that diazinon is lost from soil through volatilization (Harris & Mazurek, 1966), but the rate of loss is unknown. Results of earlier studies with ^{14}C-labelled insecticide and the use of capped containers for holding treated soils indicated that volatility was of minor importance. Under field conditions, co-distillation, high temperatures and exposed surface areas probably contribute to a greater loss of the insecticide through volatilization.

Rate estimations according to the Atkinson incremental method indicate that diazinon is rapidly degraded by hydroxyl radicals in the atmosphere. The tropospheric half-life of diazinon lies between 1.3 and 1.5 h (Stamm, 1994).

4.1.2 Movement in soil

A study concerning degradation rate and mobility of diazinon in a thatch layer of turf grass and in the underlying soil (2.5 cm) was performed by Sears & Chapman (1979). Immediately following the pesticide application, 2200 litres of water were applied to the total treated area of 80 m^2. Fourteen days after the application, less than 2% of the compound remained in the grass-thatch layer, and less than 1% in the root zone and in the underlying soil. The authors concluded that the compound readily disappeared by degradation and/or volatilization. However, it must be considered that only the top 2.5-cm layer was analysed.

The movement of diazinon and other organophosphorus compounds in the soil was evaluated by means of soil thin-layer chromatography (Sharma et al., 1986). The experiment was performed with two types of soil (silt loam and sandy loam) showing different percentages of organic matter (1.05 and 0.35%, respectively). The authors found a generally poorer movement of diazinon in the silt loam soil, probably due to the higher organic matter content and higher cation exchange capacity. When natural soils were used as

adsorbent and distilled water as eluent, diazinon showed relatively high mobility. In this study, the effects of pH and the presence of leachates of alkaline and saline salts were also evaluated. Diazinon showed a slight decrease of mobility in both soils at pH 4, whereas at pH 10 there was increase mobility in the silt loam and slight decrease in mobility in the sandy loam. The effects of leachate salt were not significant, with the exception of calcium sulfate, which decreased mobility in the silt loam soil.

The adsorption and mobility of diazinon in 25 Spanish soils and the influence of soil properties on both processes were studied (Arienzo et al., 1994). Adsorption constants of diazinon in the soils were measured using soil thin-layer chromatography and soil column leaching. The experiments were conducted with ^{14}C-labelled diazinon. Adsorption of diazinon was found to follow the Freundlich adsorption equation. The Freundlich adsorption constant (K) ranged from 0.70 to 25.73. Adsorption was highly significantly correlated ($p < 0.001$) with the content of organic matter (OM). The median K_{OM} value was 290 corresponding to a K_{OC} value of 500. There was also a significant correlation ($p < 0.01$) of K and the distribution coefficient K_d with the silt-plus-clay content in soils with low organic material content (<2%). On the basis of the soil thin-layer chromatography experiments, diazinon was found to be slightly mobile in 80% and immobile in 20% of the soils studied. In the soil column experiment, the pesticide was quite mobile under saturated flow in soils of light texture containing little organic matter. Under non-saturated flow conditions, which are more similar to natural conditions, diazinon should not be easily leached from the studied soils to groundwater.

4.2 Degradation

4.2.1 *Degradation in soil*

Seyfried (1994) studied the degradation of diazinon in an agricultural soil (silt loam, USDA) under various experimental conditions. At 20 °C and a soil moisture of 60% of the field capacity, the DT_{50} was 5 days and DT_{90} 22 days. The main metabolite, 2-isopropyl-4-methyl-6-hydroxy pyrimidine, occurred transiently and degraded with a DT_{50} of 20 days. Mineralization accounted for 86% of the applied diazinon within the experimental period of 120 days. Whereas the application rate did not influence the degradation rate, there was a dependence on temperature (DT_{50} of 12 days at 10 °C) and

soil moisture (DT_{50} of 8 days at 30% field capacity). Under sterile conditions, the DT_{50} was increased to 118 days at 20 °C and 60% field capacity. This suggests that the main route of soil degradation is microbial.

Getzin (1968) studied persistence of diazinon in soils and measured loss in autoclaved and non-autoclaved soil at several temperatures, moisture contents and pH levels under controlled laboratory conditions. Microorganisms and non-biological factors affected the persistence of diazinon in Sultan silt loam. Diazinon was primarily degraded through non-biological pathways. Although diazinon was not metabolized to any great extent by microorganisms in Sultan silt loam, it is known that soil microflora are capable of degrading the insecticide. Gunner et al. (1966) isolated a bacterium from soil that utilized diazinon as a source of sulfur, phosphorus, carbon and nitrogen, but the importance of this microorganism as a contributor to the metabolism of the insecticide in soil was not determined.

Miles et al. (1978) demonstrated that diazinon can accumulate and persist in organic soils for more than a year. It was also shown that diazinon can move from its soil-bound form into the aqueous environment either via leaching or by direct soil erosion (Miles & Harris, 1978a). Morganian & Wall (1972) demonstrated that diazinon treatment of a marine salt marsh led to a build-up of diazinon in salt marsh sod and mud.

At pH 6.8, the time required for 50% loss of diazinon is 6 weeks in autoclaved soil and 18 weeks in buffered water. Mortland & Raman (1967) demonstrated the catalytic hydrolysis of diazinon in $CuCl_2$ solutions and Cu-montmorillonite suspensions. Catalytic reactions of this nature may occur in soil, but attempts to demonstrate this phenomenon in Sultan silt loam have so far failed. Moisture variations from 50 to 100% of the moisture equivalent did not appreciably alter the degradation rates of diazinon. Variations in soil temperature between 10 and 30 °C resulted in a 4- to 10-fold difference in the time required for 50% loss of the insecticides in soil. The non-biological degradation of diazinon increased with increased acidity.

Schoen & Winterlin (1987) have studied the factors affecting the rate of diazinon degradation in soil. These are pH, soil type, organic amendments, soil moisture and pesticide concentration. Of the soil

factors investigated, the conditions for diazinon degradation in pesticide mixtures were optimum when the pesticides were present at low concentrations in moist soil, amended with peat and acidified to pH 4. Degradation was least at high pesticide concentration in neutral or alkaline mineral soil.

Utilization of diazinon by an *Arthrobacter* species and a *Streptomyces* species has been shown to alter the microbial population by stimulating a selective enrichment of these species. The *Arthrobacter* species previously reported to attack the side chain of the molecule was unable to metabolize completely the ring portion of the molecule. Similar results demonstrated that the *Streptomyces* species, too, could not by itself convert pyrimidinyl carbon to carbon dioxide. When, however, both the *Arthrobacter* and *Streptomyces* organisms were incubated together, 15-20% of the ^{14}C appeared as labelled $BaCO_3$ after 18 h, suggesting a synergistic relationship between these two organisms in attacking the pyrimidinyl portion of diazinon (Gunner & Zuckerman, 1968).

Barik & Munnecke (1982) demonstrated that a bacterial enzyme can hydrolyse diazinon in soil. In their research, an enzyme was obtained from a *Pseudomonas* sp. that could hydrolyse diazinon and several other methoxy- or ethoxy-substituted organophosphates. In this experiment, diazinon, either in 25% EC formulations or as a technical grade chemical, was enzymatically hydrolysed in an agricultural sandy soil when present at concentrations up to 1%. The degradation rate was approximately proportional to enzyme concentration up to 12 units per 20 g soil. This indicates that the initial rate of diazinon degradation is directly dependent on enzyme activities, and not on chemical or physical parameters of the soil-pesticide interactions. Although the enzyme was examined only in one soil, it is expected that it could also operate on cement or asphalt type surfaces, as well as on synthetic polymers such as carpet.

Al-Attar & Knowles (1982) studied the uptake, metabolism and elimination of diazinon in *Panagrellus redivivus*, a free-living soil nematode, and *Bursaphelenchus xylophilus*, a plant parasitic nematode. Nematodes were exposed to a solution of diazinon labelled with radiocarbon. Both nematode species metabolized diazinon, although *P. redivivus* was more active. Metabolites from *B. xylophilus* included *O,O*-diethyl *O*-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphate or diazoxon and pyrimidinol. Radioactivity accumulated to

a greater extent in *B. xylophilus* than in *P. redivivus*. Elimination of radiocarbon was more rapid with *P. redivivus* than with *B. xylophilus*, and this resulted in the presence of high levels of the polar pyrimidinol metabolite in the incubation medium of *P. redivivus*.

4.2.2 Degradation in water

Keller (1983) investigated the degradation of diazinon in samples of pond and river water, each containing 1% of sediment. Diazinon was degraded with a DT_{50} of 7 to 10 days in the pond system and 8 to 15 days in the river water. Mineralization accounted for >60% of the applied material within 7 weeks in both systems.

In a mesocosm study conducted with 17 treated and 4 untreated ponds (0.05 hectare each), diazinon degraded rapidly. The disappearance half-lives averaged 5.2 to 12.2 days (Giddings, 1992).

Kanazawa (1975) found diazinon to be fairly persistent in tap water in a glass aquarium, degrading to 27% in 30 days.

Ferrando et al. (1992) studied the persistence of diazinon in natural water from Albufera Lake and in experimental water from their laboratory. Degradation was faster in lake water, the half-lives being 70 and 79 h for lake and laboratory water, respectively. The degradation process in both media was comparable until 96 h. The authors found 43.5 and 49.4% of the applied diazinon in natural and experimental water, respectively, at 96 h.

4.2.3 Bioconcentration

4.2.3.1 *Fish and aquatic invertebrates*

The bioconcentration factors (BCF) of diazinon over a 7-day period were as follows: topmouth gudgeon 152; carp 65; guppy 18; crayfish 4.9; red snail 17; pond snail 5.9 (Kanazawa, 1978).

Seguchi & Asaka (1981) reported the intake and excretion of diazinon and its metabolites in freshwater fish, and the relationship between the BCF of diazinon and fat content of fish. During exposure to continuous-flow water containing 0.02 mg diazinon/litre the concentration of diazinon in fish rapidly increased, reaching a maximum after 3 days. Thereafter, the diazinon concentration slightly

decreased and remained at equilibrium. The BCFs for carp, rainbow trout, leech and shrimp at equilibrium were 120, 63, 26 and 3, respectively. As for the metabolites, pyrimidine analogue was found in all fish species, but diazinon and related compounds were found only in carp and rainbow trout. The concentration of the metabolites reached a maximum after 3-7 days exposure to diazinon. Diazinon was metabolized to diazoxon in the channel catfish liver microsomal enzyme system, but it was not found in any other fish species. When the fish were transferred to clean water, diazinon and its metabolites were rapidly lost from the fish. Seven days after being transferred to clean water, the diazinon concentration decreased to 0.3-8.0% of the equilibrium concentration, and the metabolites decreased below the detection limit.

Similar results have been observed for topmouth gudgeon by Kanazawa (1975, 1978). A linear relationship was observed between the bioconcentration ratio and fat content in fish. Seguchi & Asaka (1981) identified six metabolites of diazinon, and Fujii & Asaka (1982) identified another three: hydroxydiazinon, hydroxymethyl diazinon and isopropenyl diazoxon.

The toxicity, accumulation and elimination of diazinon were investigated in the European eel (*Anguilla anguilla*). Fish exposed to sublethal concentration (0.042 mg/litre) accumulated diazinon in the liver and muscle tissues. The BCFs for diazinon were 1859 in liver and 775 in muscle over the 96-h exposure period. When removed from diazinon-containing water, the contaminated fish rapidly eliminated diazinon. The excretion rate constants were 0.108 per h for liver and 0.016 per h for muscle. Diazinon half-lives were 16.6 and 33.2 h for liver and muscle, respectively (Sancho et al., 1992).

The freshwater fish Motsugo (*Pseudorasbora parva*) was reared in an aquarium tank containing about 1 mg diazinon/litre for 30 days. The persistence of the insecticide in water and the uptake and excretion of the insecticide by fish were monitored. Diazinon degraded by 72% in 30 days. The concentration of diazinon in fish reached a maximum level of 211 mg/kg after 3 days. Afterwards, the concentration of the insecticide decreased gradually due to metabolism and excretion (Kanazawa, 1975).

Bioconcentration and excretion of diazinon were studied in the carp (*Cyprinus carpio* L.). The average BCF values for diazinon were

20.9 in muscle, 60.0 in liver, 111.1 in kidney and 32.2 in gall bladder over a 168-h exposure period. The excretion rate constants of diazinon (ng/g per h) were 0.002-0.024 for muscle, 0.001-0.020 for liver, 0.0004-0.004 for kidney and 0.002-0.023 for gall bladder, respectively (Tsuda et al., 1990).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 Air

The amount of insecticide present in the air of commercial pest control buildings, service vehicles and food preparation-serving areas following routine commercial insecticide application has been measured. Diazinon was measured in the ambient air of storage and office rooms in six North Carolina (USA) firms in a 4-h period. In the storage rooms the mean value was 284 (85-837) ng/m^3 air and in the offices 163 (31-572) ng/m^3 air. Diazinon was also detected in the ambient air of vehicles used in commercial pest control activities. Mean diazinon concentrations (ng/m^3 air) in 2-h of sampling from six vehicles were 88 (7-239) in sedans and 171 (11-543) in vans, the mean value being 130 (7-543). The highest level of diazinon detected in the ambient air of offices of pest control building was far below the allowable limits (TLV : 100 µg/m^3) (Wright & Leidy, 1980).

Wright et al. (1982) studied the amount of diazinon in cabs of stationary pick-up trucks used by the pest control service. Additional air samples, taken while the same pick-up truck was moving, provided data for comparison of insecticide levels in individual pick-up trucks when moving and stationary. Diazinon was present in significantly greater concentrations than chlorpyrifos. This may be attributable to the facts that the service technicians kept diazinon in sprayers during the sampling periods and that they used it in servicing accounts during the sampling day. It could therefore have contaminated their clothing and skin and passed into the air when they were in the pick-ups. The maximum diazinon detected was 5.15 µg/m^3 for a 2-h period or 20.6 µg/m^3 for an 8-h period, which is about 1/5 of the allowable limit. However, the amount of airborne diazinon to which a technician was actually exposed during a working day was even less than 20.6 µg/m^3, since the maximum time any technician spent in a pick-up was 3.8 h.

Wachs et al. (1983) reported the concentration of diazinon in the air of a retail garden store that sold the insecticide. The concentration found in the air based on the 14-h period pumping through the polyurethane filters was 3.4 µg/m^3. All of the diazinon was found in

the polyurethane plug closest to the air inlet. Diazinon was not found in the second plug or unused plugs which were similarly Soxhlet-extracted and analysed. It was concluded that the concentration of diazinon in air depended on a number of factors, including the type of formulation, air temperature, type and condition of containers, prior spills and types of floor covering. The concentration of diazinon vapour found in this study would not appear to constitute a hazard to store personnel or customers.

Airborne concentrations of diazinon were measured in rooms for 21 days after crack and crevice application. Residue levels were greatest in treated rooms (38 $\mu g/m^3$) followed by adjacent (1 $\mu g/m^3$) and upper and lower floor rooms (about 0.4 $\mu g/m^3$). Low levels of diazinon were detected in all rooms 21 days after application. Small amounts of diazinon (corrected to an 8-min application period) were detected on respirator pads (2.6 μg) and waist pads (2.3 μg) worn by the applicator (Leidy et al., 1982).

Airborne and surface concentrations of diazinon were measured at intervals up to 10 days after broadcast spray application onto the floors of seven offices. Diazinon concentrations peaked 4 h after application at 163 and 27 $\mu g/m^3$ of air sampled, respectively. Airborne concentrations of diazinon indicated that building occupants should not enter unventilated rooms for at least 2 days after spraying. Residues on aluminium plates and furniture were examined at intervals of up to 48 h after spraying, and in many cases the surface concentrations were higher at 24 or 48 h after spraying than at one hour. The peak residue concentration of diazinon was 38 ng/cm^2 of surface area sampled at 48 h (Currie et al., 1990).

5.1.2 Water

Insecticide residues on suspended and bottom sediments of streams of Ontario, Canada, have been studied in a tobacco-growing, vegetable muck area. Bed load samples contained three to six times higher concentrations of insecticides than bottom material (Miles, 1976).

From 1985 to 1987, a monitoring survey was conducted to determine the levels of selected pesticides in farm ditches located in the lower mainland of British Columbia, Canada. Diazinon was not detected in ditch water (detection limit = 1 μg/litre). In ditch

sediments, diazinon was sporadically found at concentrations up to 4 μg/kg (detection limit = 1 μg/kg) (Wan, 1989).

During the first half of 1984, diazinon was not detected in raw or treated water samples from the Lakeview and Lorne Park Water Treatment Plants in Toronto, Ontario (detection limit = 10 ng/litre) (MacLaren Plansearch Inc. & FDC Consultants Inc., 1985).

Detectable concentrations of diazinon occurred in less than 0.1% of water samples collected from 11 Southern Ontario agricultural watersheds during 1975-1977. The concentration was mainly below 0.01 μg/litre, the maximum value being 0.15 μg/litre (Frank et al., 1982).

Sampling performed in 1992 by the United Kingdom National Rivers Authority showed diazinon at >0.1 μg/litre in 74 out of 2300 fresh water samples and at > 0.15 μg/litre in 1 out of 12 seawater samples.

5.1.3 Soil

In 1971 hay and soil samples were collected in 9 states in the USA to determine the incidence and levels of pesticide residues in hayfields. Residues were detected in 8% of the soil samples and 29% of the hay samples. Diazinon was detected in four hay samples (Gowen et al., 1976).

In 1976, soil samples from 28 farms located in six vegetable growing areas of southwestern Ontario, Canada, contained diazinon residues from trace amounts (< 0.02 mg/kg) to 0.29 mg/kg (Miles & Harris, 1978b).

5.1.4 Fruit, vegetables and food

Results of supervised trials and monitoring of diazinon residues in or on food and feed commodities have been comprehensively reviewed and summarized (FAO/WHO, 1994a). The following examples indicate that diazinon residues are generally low.

Ward et al. (1972) performed a study to determine the rate of decline of diazinon residue on wheat in Texas, USA. There was a steady decline in the amount of diazinon remaining on foliage samples

after application. Only 0.16 mg/kg and 0.31 mg/kg remained 28 days after treatment with 0.28 and 0.56 kg a.i./ha, respectively. Harvest samples showed that less than 0.05 mg/kg remained in either the foliage or grain.

Between 1978 and 1986, 305 samples of apples were analysed for residues of a wide range of pesticides used in their production. Residues of diazinon were found occasionally. They were well below the maximum residue limit and correlated well with the pattern of use (Frank et al., 1989).

Between 1986 and 1988, 433 composite vegetable samples representing 16 commodities, which were treated by various pesticides including diazinon, were collected from farm deliveries to the marketplace in Ontario, Canada. All samples were analysed for insecticides and fungicides. The commodities tested included asparagus, beans, carrots, celery, cucumbers, lettuce, onions, peppers, potatoes, radishes, rutabagas and tomatoes. In 64% of samples, no pesticide residues were identified (the limits of detection ranged from 0.005 to 0.05 mg/kg). A further 22% had combined insecticide and fungicide residues below 0.1 mg/kg. Only three samples (0.7%) had residues that exceeded the Maximum Residue Limit (MRL). These involved diazinon on celery. While some commodities had no detectable residues, others had measurable residues of up to three different pesticides. The highest levels were found on celery, lettuce and field tomatoes (Frank et al., 1990).

Levels of diazinon permitted in the USA on human food range from 0.1 mg/kg in potatoes to 0.7 mg/kg in most leafy vegetables. During the course of pesticide surveillance of vegetables, an unknown analytical response in spinach extract was seen, which was subsequently identified as diazinon metabolite (2-isopropyl-4-methyl-pyrimidin-6-ol). Cairns et al. (1985) described an analytical procedure adapted to confirm both diazinon and its metabolite in spinach, at very low levels, by methane chemical ionization mass spectrometry. The presence of this metabolite at the 1 mg/kg level represents an order of magnitude greater than that found for diazinon itself.

In a study of diazinon residues in prepared foods, accidentally exposed during and following treatment, the amounts of diazinon residues in food left in the room for 30 min after treatment ranged from 0.02 to 0.05 mg/kg. No detectable residues of diazinon were

found in the potatoes or dinners placed in the rooms 4.5 h after treatment and removed after 5 h. A person consuming a dinner at the highest residue found would have ingested 0.0153 mg of diazinon. For a person weighting 70 kg this would amount to 0.218 µg/kg (Jackson & Wright, 1975).

5.1.5 Milk

Insecticides in polyvinyl chloride pellets were included in a commercial dairy protein supplement and fed to dairy cows at 1.4, 2.0 and 2.5 mg of diazinon/kg body mass for 2 weeks. No insecticidal residues were found in milk samples collected at 1, 3, 7, 10 or 14 days. Even 2.5 mg/kg dosage would provide a 5-fold margin of safety for PVC formulation-diazinon fed to cattle to control face fly larvae in manure (Lloyd & Matthysse, 1971), and diazinon-PVC was found to be still a highly effective larvicide if given at the dose of 0.5 mg insecticide/kg per day (Lloyd & Matthysse, 1966, 1970).

Derbyshire & Murphy (1962) reported no diazinon residues in milk from cows fed 10 mg/kg body weight for 7 days. Robbins et al. (1957) found only traces of radioactivity in a cow's milk 6-24 h after a single oral dose of ^{32}P-labelled diazinon (20 mg/kg).

5.1.6 Meat and fat

Tissue residues were determined and toxicity symptoms were noted after lambs were sprinkled and dipped with 0.06% diazinon emulsion or sprinkled with 1% diazinon emulsion. The only diazinon residues found were 1.45-2.30 mg/kg in fat, 1 day after dipping in 0.06% diazinon, with concurrent 44-47% plasma cholinesterase activity depression. Low residues were present in blood from these sheep. Most tissues contained no detectable diazinon at 15 or 26 days after lambs were dipped in 0.06% diazinon, but fat contained up to 0.52 mg/kg at 15 days and 0.31 mg/kg at 26 days. Sprinkling with 1% diazinon produced no residues in most tissues. A maximum of 23 mg/kg was found in fat. The only clinical poisoning involved a 3-day-old lamb dipped in 0.12% diazinon suspension. Lambs more than 1 week old were not poisoned by 0.06% diazinon nor were lambs more than 1 month old when treated by 0.25% diazinon (Matthysse et al., 1968).

Harrison et al. (1962) found 0.4 mg diazinon/kg in meat of unshorn sheep 1 day after dipping in 0.05% diazinon emulsion. This decreased to 0.25 mg/kg and 0.16 mg/kg at 4 and 7 days after dipping, respectively, and there were negligible amounts 25 days after dipping.

Claborn et al. (1963) found 0.69 mg/kg in beef fat 1 day after the last of 11 weekly spraying with 0.05% diazinon suspension. The authors reported a rapid loss of diazinon from beef fat and the amount of residues were negligible 14 days after spraying.

Samples obtained from retail outlets in the United Kingdom during 1984-1986 generally showed zero or low levels of diazinon residues. Diazinon was not detected in samples of beef, imported lamb, pork or veal, but low levels were found in United Kingdom lamb in 1984/1985 (up to 1.7 mg/kg) and 1985/1986 (up to 0.1 mg/kg). Samples of fat taken in 1986 were analysed and, out of 274, 19% contained diazinon. In 1987, however, out of 280 samples analysed, 7% contained diazinon and in four of them residues exceeded the Codex MRL of 0.7 mg/kg fat. Diazinon was not detected in butter, milk or cheese (MAFF, 1989).

Various pesticides and pollutants were examined in poultry meat from Israel. The levels of these, which included diazinon in broilers, turkeys and geese, were said to be extremely low and below the USA tolerance levels (Kathein, 1986)

5.2 General population exposure

The primary exposure to the general population will be through intermittent dietary exposure and inhalation exposure. Exposure via water is negligible. Total-diet studies commenced in the United Kingdom in 1966. In the second survey (1970-1971) and in the latest survey (1985-1988), diazinon residues were not detected (Egan & Weston, 1977; MAFF, 1982, 1986, 1989). Findings similar to those in the United Kingdom were also made in the USA. Toddler total diets have also been the subject of investigation in the USA. Diets collected in ten American cities between 1978 and 1979 were examined. The components were drinking-water, whole milk, other dairy products and dairy substitutes, meat/fish/poultry, grain cereals, potatoes, vegetables, fruit juices, oils and fats, sugars and beverages (Gartrell et al., 1985a). A similar exercise in the years 1980-1982 was conducted

in 13 American cities. The results were similar to those obtained in 1978-1979, with intake of diazinon being low (Gartrell et al., 1985a,b).

A total-diet study in New Zealand was performed at 3-monthly intervals in the period 1974-1975. Of 116 samples analysed, 82 (71%) had no detectable residues of diazinon. Intakes were well below the Codex MRLs (Dick et al., 1978).

The overwhelming evidence from residue and total-diet studies suggests that residues of diazinon are generally within the acceptable levels set by the Codex Alimentarius Commission. The results suggest that the compounds are rapidly broken down, whether on plants or in animals, further reducing the risks to humans (IPCS, 1986).

During a 5-year study period (1981-1986), the US Food and Drug Administration analysed nearly 20 000 domestic and imported samples of food and feed commodities for pesticide residues. The results showed that 29 out of 6391 domestic agricultural commodities and 35 out of 12 044 imported agricultural commodities had diazinon levels greater than 0.05 mg/kg (Hundley et al., 1988).

Diethyl phosphate (DEP), an organophosphate metabolite, was found in the urine of symptomatic residents who resided in a household that had been sprayed with diazinon 4.5 months earlier. Pre- and post-decontamination data with regard to symptoms and to DEP, cholinesterase, and surface and air levels underscore the utility of alkyl phosphate metabolites for monitoring exposure. The data also emphasize the efficacy of clean-up measures when baseline data are not available to determine if "within-normal" cholinesterase levels are, in fact, depressed (Richter et al., 1992).

5.3 Occupational exposure

An occupational exposure study was conducted for a firm employing 22 pest control operators (PCOs) exposed to three organophosphorus insecticides including diazinon. The 8-h exposure levels were less than 131.0 $\mu g/m^3$. Urine samples (24-h) were analysed for alkyl phosphates and showed the presence of metabolites for these three insecticides. The effect of this exposure was reflected by a statistically significant inhibition of plasma cholinesterase activity

among the PCOs, but physical examinations detected no apparent toxic effects (Hayes et al., 1980).

A behavioural evaluation of pest control workers with short-term (mean 39 days) low-level exposure to diazinon was conducted in 1985 during the course of a pest control program in California (see section 8.2.2). The diazinon metabolite diethylthiophosphate (DETP) was measured in pre- and post-shift urine samples and the full-shift exposure to diazinon was quantified for 19 subjects using personal air monitoring and passive badges. The median diazinon exposure was 2.1 mg/day (Maizlish et al., 1987).

An investigation was conducted to determine worker exposure to airborne pesticides during tree and ornamental shrub applications using hand-held equipment during an entire work shift. Employee exposure data were collected for 3 consecutive years. The sampling was performed during the late spring, summer and early autumn when insect and disease activity was most prevalent. Sampling was conducted at 23 locations. Those applying these chemicals sustained low-level exposure to acephate, benomyl, carbaryl, chlorothalonil, diazinon and dicofol. As pesticide label instructions for mixing and applying pesticides were strictly followed, the tree and ornamental shrub applicators were able to keep inhalation exposures below the levels recommended by OSHA and NIOSH. Of the 74 exposures monitored, 67% were below the detection limit (0.001 mg/m^3), while others were 0.001-0.040 mg/m^3. This observation supports the correctness of not including specific respiratory protection measures on pesticide label directions for mixing, loading and applying these pesticides (Leonard & Yeary 1990).

Dermal, respiratory and urine measurements were made on workers applying granular diazinon pesticide formulation. In all, 15 workers and four control subjects were monitored. The workers applied the compound in yards and small pastures using hand equipment comparable to that used in a home environment. Respiratory air samples, ethanol hand rinse samples, clothing patch samples and urine samples were collected. The diazinon exposures were correlated with job category, application duration, application equipment and protective clothing. The best determinants of diazinon exposure were the job categories and the use of the belly grinder type of spreader. The rank of exposure magnitude, from highest to lowest, was the crew using the belly grinder, the crew not using the belly

grinder, the crew chief and the supervisor. The mean daily dermal and respiratory diazinon exposures for these four job categories ranged from 0.6 to 11 mg, 0.1 to 1.8 mg, 0.1 to 0.25 mg, and 0.03 to 0.07 mg, respectively. The amount of urinary diethylthiophosphate increased during the day for all job levels, but showed variable recovery (Weisskop et al., 1988).

6. KINETICS AND METABOLISM

6.1 Absorption, distribution and excretion

6.1.1 Oral administration

6.1.1.1 Rats

Four male and 2 female Wistar rats were treated with single oral doses of 0.8 mg [pyrimidine-^{14}C]-diazinon (specific activity 4.0 μCi/mg). An additional group of 4 males received [ethoxy-^{14}C]-diazinon (3.2 μCi/mg) at the same dose level. During the observation period of 168 h, both labelled parts of the molecule were excreted almost completely, 65.4-80.0% of the administered radioactivity being detected in urine, 16.0-23.5% in the faeces and, with the ethyl-label, 5.6% in the expired air (total recovery 90.2-98.3%). No radioactive CO_2 was detected with the pyrimidine label. The half-life times of excretion were 7 h with the ethyl label and 12 h for both sexes treated with the pyrimidine-labelled material. Daily oral administration of 0.1 mg [pyramidine-^{14}C]-diazinon to male rats for 10 consecutive days resulted in no accumulation of the radioactivity in any organ investigated (oesophagus, stomach, intestines, liver, spleen, pancreas, kidneys, lungs, testes, muscles, fat). Six hours after the last administration, the highest residues were detected in the muscles (0.77% of the totally applied dose), caecum (0.76%) and small intestine (0.65%). The residues were below the detectable limit 48 h after the cessation of the treatment (Mücke et al., 1970).

Sprague Dawley rats received [pyrimidine-^{14}C]-diazinon at single oral doses of 10 mg/kg (specific activity 30.3 μCi/mg) or 100 mg/kg (specific activity 9.7 μCi/mg). A third group was treated with daily oral doses of 10 mg/kg technical diazinon (87.7% pure) for 14 consecutive days, followed by a single treatment at the same dose level with the ^{14}C-labelled compound. The disposition of the administered ^{14}C was observed for a 7-day period before the animals were killed and the tissues removed for analysis. The average recovery of the radioactivity was 99.2%. Elimination of diazinon equivalents was rapid. In the low-dose group, males and females eliminated 93 and 86%, respectively, of the administered radioactivity in the urine within 24 h. Faecal elimination amounted to 1.6 and 1.1%, respectively, in the same time period. In the high-dose group, the respective values

were slightly lower and indicated that the elimination was more rapid in males (90.8% in urine and 2.2% in faeces) than in females (58.2% in urine and 0.87% in faeces). The pre-conditioning of the rats had no influence on absorption and elimination. Seven days after the administration of the [pyrimidine ^{14}C]-diazinon, the residual radioactivity was generally low. Among the tissues examined (heart, lung, spleen, kidney, liver, fat, testes, ovaries, uterus, muscle, brain, blood plasma, blood cells, bone), the residual radioactivity amounted to approximately 0.01 mg/kg diazinon equivalents in the low-dose group; only fat (0.02 mg/kg), blood cells (0.05 mg/kg) and bone (<0.017 mg/kg) contained higher amounts of radioactivity. In the high-dose group, the residual radioactivity was 8-10 times higher. Pretreatment with technical diazinon for 14 days led to residues similar to those observed in the low-dose group (Craine 1989a,b).

6.1.1.2 *Guinea-pigs*

Male guinea-pigs treated orally with 45 mg/kg [^{32}P]-diazinon (specific activity 117-197 cpm/mg) in peanut oil, the tissue distribution was determined at 2, 4, 8 and 16 h after treatment and the excretion of ^{32}P was investigated over an 8-day period. Following oral administration, the compound was rapidly absorbed as shown by a sharp decrease of activity in the stomach and low levels found in the small intestine. Within 16 h, 46.6% of the administered radioactivity was eliminated in the urine and 0.34% appeared in the faeces. The caecum showed a gradual increase of radioactivity, 13-36% of the administered dose accumulating in the caecum over 16 h after the administration. Irrespective of this accumulation, within 48 h after dosing, 80% of the administered radioactivity was eliminated in the urine while only 8% was eliminated in the faeces (Kaplanis et al., 1962).

6.1.1.3 *Dogs*

Two female Beagle dogs were intravenously dosed with 0.2 mg/kg [ethoxy-^{14}C]-diazinon (specific activity 3.4 μCi/mg) in 0.7 ml ethanol. Blood samples were drawn at times ranging from 5 min to 7 h after the injection. The decline of the radioactivity in the blood was biphasic with a slower second phase. The half-life of elimination from blood for this second phase was calculated to be 363 min. Approximately 58% of the administered radioactivity was recovered in the urine within 24 h after the administration. Another two female

beagle dogs were orally dosed by capsule with 4.0 mg/kg [ethoxy-^{14}C] diazinon in ethanol. Approximately 85% of the administered radioactivity was recovered within 24 h after oral administration, with 53% of it occurring in urine (Iverson et al., 1975).

6.1.1.4 Goats

Two lactating goats were orally treated with [pyrimidine-^{14}C]-diazinon (specific activity 9.7 µCi/mg) in gelatin capsules for four consecutive days at a dose level of 4.5 mg/kg per day, corresponding to a dietary exposure of 100 mg/kg of feed. During the observation period, in average 64.1% of the administered radioactivity was excreted with urine, 10.4% with the faeces and 0.31% with the milk. A plateau of radioactivity in the milk was reached after 3 days of dosing at a mean level of 0.46 mg/kg diazinon equivalent. At sacrifice, radioactivity in the blood accounted for 0.2% and the tissues examined accumulated 0.92% of the administered dose. The highest residual radioactivity was detected in the kidney (2.0 mg/kg) and the liver (1.2 mg/kg). The other tissues examined contained 0.23-0.3 mg/kg diazinon equivalents (Simoneaux 1988a,b; Pickles & Seim, 1988).

6.1.1.5 Cow

A lactating Hereford cow (body weight 268 kg) was orally treated with a gelatin capsule containing 20 mg/kg ^{32}P-diazinon (specific activity 518 cpm/µg). Urine and faeces were collected during 36 h after treatment and further samples were investigated until the study was terminated after 168 h. In addition, milk and blood samples were investigated. Within 36 h, approximately 74% of the administered radioactivity was excreted with the urine, 6.5% appeared in the faeces and 0.08% was found in the milk. A peak concentration of 2.27 mg/kg diazinon equivalents was reached 18 h after the administration (Robbins et al., 1957).

6.1.1.6 Hens

Four laying Leghorn hens were treated with 2-^{14}C-diazinon (specific activity 30.3 µCi/mg) in gelatine capsules for seven consecutive days at daily doses of 1.7 mg/kg body weight, corresponding to a dietary exposure of 25 mg/kg in feed. Excreta and eggs were collected and, approximately 24 h after the final dose, the animals were killed and tissue samples of liver, kidney, blood, lean

meat, skin and attached fat, and peritoneal fat were examined. Elimination of most of the administered radioactivity occurred via the excreta, with 78.6% of the total dose being excreted during the study period. Approximately 0.1% of the radioactivity was found in tissues and blood, less than 0.01% appeared in the egg yolks and 0.07% was detected in the egg whites. The residual radioactivity in the tissues amounted to 0.148 mg/kg diazinon equivalents in the kidney, 0.137 mg/kg in blood, 0.11 mg/kg in the liver and 0.01-0.025 mg/kg in the other tissues examined. The residues in the egg yolks ranged from 0.006 mg/kg diazinon equivalents to 0.065 mg/kg while those in the egg whites ranged from 0.038 mg/kg to 0.066 mg/kg. On a whole egg basis, a plateau concentration of 0.047 mg/kg was reached on day 4 of treatment (Simoneaux 1988c,d; Burgener & Seim, 1988).

6.1.2 Dermal application

6.1.2.1 Rats

The percutaneous absorption of diazinon was investigated in male and female Sprague Dawley rats dermally exposed to 1 mg/kg (specific activity 25.2 μCi/mg) and 10 mg/kg (specific activity 2.62 μCi/mg) of [pyrimidine-^{14}C-diazinon] dissolved in tetrahydrofuran. The dermal absorption, excretion and tissue residues were determined after 0, 2, 8, 24, 48, 72 and 144 h. At each time point, four rats per sex and dose group were used. The total recoveries for the balance data averaged 96.3-101.5%. Calculated t_{50} absorption rates (i.e. the amount of time required for 50% of the administered dose to be absorbed into or penetrate through the skin) in males and females were 11.8 and 5.2 h, respectively, at the low-dose level of 1 mg/kg. At 10 mg/kg the respective t_{50} absorption rates were 10.2 and 5.3 h, respectively, indicating that dermal absorption was more rapid in females and was dose-dependent. The urine was the major route of excretion in both sexes at both dose levels, 65-78% of the radiolabel being excreted within 72 h. Times for 50% excretion in males and females dosed at 1 mg/kg were 28.1 and 26.8 h, respectively. In the high-dose groups the times for 50% excretion were 24.1 and 20.3 h in males and females, respectively. The residual radioactivity in tissues reached a maximum at 8 h after the administration in both dose groups (plasma, red blood cells, fat, brain, muscle, lung, heart, spleen, kidney, liver, stomach, small and large intestines, gonads, skin wash and dissolved skin were assayed). In the low-dose group of males after 8 h, highest values were found in stomach (0.36 mg/kg diazinon

equivalents), small intestines (0.16 mg/kg), kidney (0.15 mg/kg), liver (0.1 mg/kg) and skin (3.9 mg/kg in the skin wash and 0.86 mg/kg in the dissolved skin). Reflecting their absorption rate, the females of the low-dose group showed slightly higher tissue levels and a lower residual radioactivity in the skin wash. After 144 h, residues were down to the limit of quantification in most tissues, in both dose groups and in both sexes (Ballantine, 1984).

6.1.2.2 *Sheep*

Two sheep were dermally treated with [pyrimidine-^{14}C-diazinon] (specific activity: 3.7 µCi/mg) dissolved in acetone for three consecutive days. In order to mimic an extreme maximum exposure in a dermal treatment of 40 mg/kg, 2270 mg ^{14}C-diazinon was applied daily to a shaved area of the back that constituted approximately 10% of the animal's surface area. The area of application was left uncovered. Six hours after the last administration the animals were killed and heart, liver, kidney, back fat and leg muscle were analysed. The tissue extractability was greater than 90% for all tissues. The highest average residues were detected in kidney (9.4 mg/kg diazinon equivalents) and back fat (7.3 mg/kg), while levels in heart, liver and leg muscle amounted to 4-4.4 mg/kg (Capps, 1990; Pickles, 1990).

6.1.2.3 *Humans*

The dermal absorption of diazinon in humans is much less than in rats. Six volunteers were dermally treated with [pyrimidine-^{14}C]-diazinon on the ventral forearm or the abdomen. The test material was administered in acetone solution (2 µg/cm^2) or dissolved in lanoline wool grease (1.47 µg/cm^2) over a 10-cm^2 area of the skin without occlusion. After 24 h, the test substance remaining on the site of administration was washed off and the renal elimination followed for seven days. Independent of the vehicle and the site of administration, only 3-4% of the dose applied was percutaneously absorbed (Wester et al., 1993).

6.1.3 *Other routes*

6.1.3.1 *Intraperitoneal administration*

The tissue distribution of diazinon and the inhibition of cholinesterase (ChE) activities in plasma and erythrocytes were

investigated using male rats that received a single intraperitoneal dose of diazinon (100 mg/kg body weight) in olive oil. The blood diazinon level was estimated to reach a maximum at 1-2 h after intraperitoneal administration. It was demonstrated that the diazinon residue levels were highest in the kidney, when comparing the distribution of diazinon among liver, kidney and brain in the animals after dosing. Erythrocyte and plasma ChE activities were inhibited rapidly, but ChE inhibition was greater in the erythrocytes than in plasma (Tomokuni & Hasegawa, 1985).

The tissue distribution of diazinon and the inhibition of ChE activities in plasma, erythrocyte and brain was investigated using male rats and mice that received a single intraperitoneal (i.p.) dose of diazinon (20 or 100 mg/kg body weight) in olive oil. The blood diazinon level was estimated to reach a maximum 1-2 h after the i.p. administration. It was demonstrated that the diazinon residue levels were highest in the kidney, when comparing the distribution of diazinon among liver, kidney and brain in the animals after dosing. The ChE inhibition by diazinon exposure was greater in the plasma than in the erythrocytes for male mice, while its inhibition was greater in the erythrocytes for male rats. Brain ChE activity was also inhibited markedly in the mice after dosing (Tomokuni et al., 1985).

6.1.3.2 *Subcutaneous administration*

Male guinea-pigs were subcutaneously treated with 45 mg/kg ^{32}P-labelled diazinon (specific activity -117-197 cpm/μg) in peanut oil. The tissue distribution was determined 2, 4, 8 and 16 h after treatment, and excretion of ^{32}P was investigated over an 8-day period. Following subcutaneous administration, urinary elimination amounted to 20% of the administered dose after 16 h. The levels of radioactivity found in the gastrointestinal tract were low apart from the caecum, which accumulated up to 5.5% of the administered dose over 16 h. After 48 h, urinary elimination amounted to about 60%, while only trace amounts were eliminated with the faeces (Kaplanis et al., 1962).

6.1.3.3 *Intravenous administration*

Four female Rhesus monkeys were dosed intravenously with 2.1 μCi (31.8 μg) [pyrimidine-^{14}C]-diazinon dissolved in propylene glycol. Within 7 days, average values of 56 and 23% of the dose were eliminated in urine and faeces, respectively (Wester et al., 1993).

6.2 Metabolism

The metabolic fate of diazinon was studied with different modes of administration using unlabelled and radiolabelled diazinon in various species including rat, mouse, guinea-pig, dog, sheep, goat, cow and chicken. Additional *in vitro* experiments were conducted using tissue slices or cell fractions. A comparative summary of the results available was provided by Hagenbuch & Mücke (1985). In all species tested, diazinon was rapidly and almost completely absorbed from the gastrointestinal tract. It was also absorbed from the skin.

The main metabolic pathways of degradation of diazinon are:

a) Cleavage of the ester bond of diazinon or diazinoxon leading to the hydroxypyrimidine derivatives.

b) Transformation of P-S moiety to the P-O derivative, leading to the active metabolite, diazoxon.

c) Oxidation of isopropyl substituent leading to the corresponding tertiary and primary alcohol derivatives.

d) Oxidation of the methyl substituent leading to the corresponding alcohol.

e) Glutathione-mediated cleavage of the ester bond leading to a glutathione conjugate.

The hydrolytic and oxidative cleavage of the phosphorus ester bond, leading directly or via diazoxon to the pyrimidinyl derivative, play the most prominent role in the metabolism of diazinon. Glutathione conjugation appears to be of small importance. Metabolites maintaining the phosphorus ester bond are of transient nature and are only observed in minor quantities.

The general metabolic pathways of diazinon in mammals are given in Fig. 1.

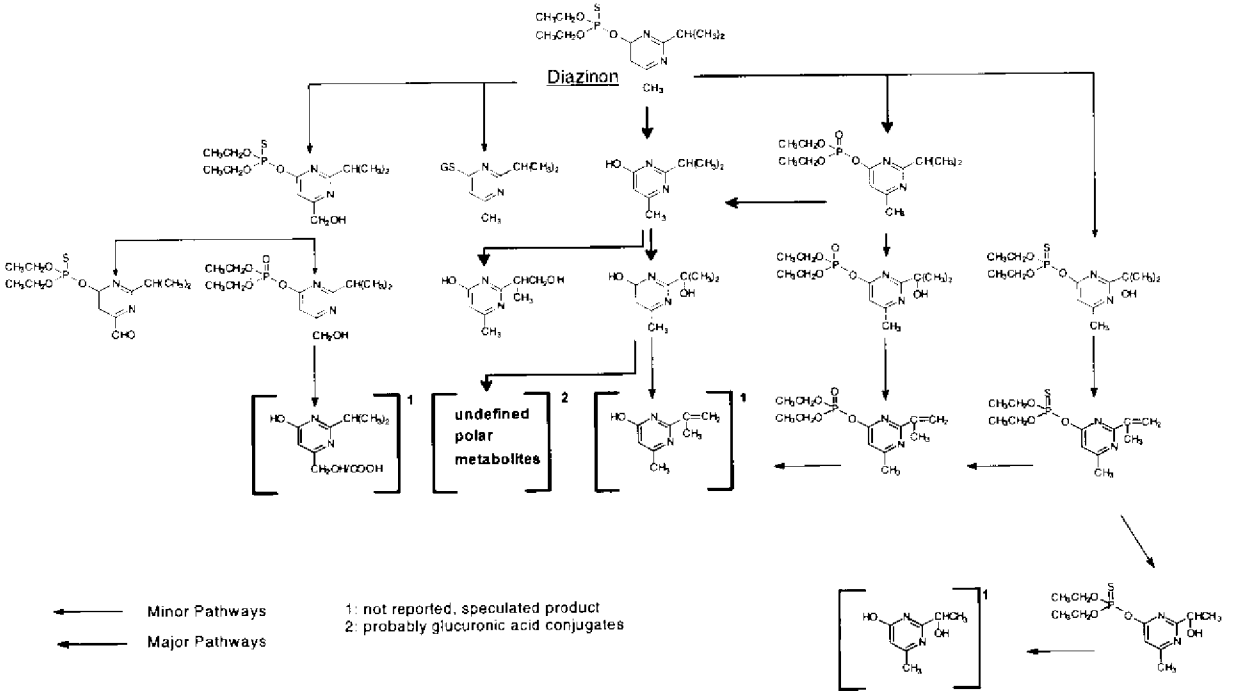


Fig. 1. Metabolic pathways of diazinon in mammals.

The metabolites formed, i.e. diethylphosphoric acid, diethylthiophosphoric acid and the derivatives of pyrimidinyl ring, are eliminated mainly via the kidneys. Only minimal quantities of the metabolites were detected in milk and eggs.

6.2.1 In vivo *metabolic transformations*

6.2.1.1 *Mice*

When male ICR mice (number not stated) were treated orally with diazinon or [pyrimidine^{14}C] diazinon at 50 or 75 mg/kg body weight, one half of the high-dose animals died and the rest showed symptoms (sweating, crouching) (Miyazaki et al., 1970; Sekine, 1972). At the low dose, no signs of toxicity were observed. Metabolism and excretion occurred rapidly, and the metabolites diazoxon, *O,O*-diethyl-*O*-[2-(alpha-hydroxyisopropyl)-4-methyl)-6-pyrimidinyl] phosphorothioate, and *O,O*-diethyl-*O*-(2-(2-propenyl)-4-methyl-6-pyrimidinyl) phosphorothioate were found in the urine 1 h after treatment. Most of the metabolites were found in urine 6 h after treatment, but metabolism was not identical in the two dose groups. In the low-dose group *O,O*-diethyl-*O*-(2-isopropyl-4-hydroxymethyl-6-pyrimidinyl) phosphorothioate and *O,O*-diethyl-*O*-(2-isopropyl-4-formyl-6-pyrimidinyl) phosphorothioate were found, but this was not observed in the high-dose group. In the high-dose, but not the low-dose group *O,O*-diethyl-*O*-(2-(a-hydroxyethyl)-4-methyl-6-pyrimidinyl) phosphorothioate was found.

The metabolism of [pyrimidine-^{14}C]-diazinon and [ethoxy-^{14}C]-diazinon was investigated by Mücke et al. (1970). Four metabolite fractions were found in urine and faeces, three metabolites representing approximately 70% of the total radioactivity applied. Hydrolysis of the ester bond yielded 2-isopropyl-4-methyl-6-hydroxypyrimidine (22.5% of the applied radioactivity in urine); oxidation at the primary carbon atom produced 9% of the applied radioactivity in urine, while oxidation at the tertiary carbon atom of the isopropyl side chain produced 22%. In addition, trace amounts of unchanged diazinon were detected in faeces. No cleavage of the pyrimidine ring with subsequent oxidation of the fragments to CO_2 took place (Mücke et al., 1970).

6.2.1.2 Rats

A study by Capps (1989) investigated the diazinon metabolites in male and female rats orally treated with single doses of 10 and 100 mg/kg [pyrimidine ^{14}C]-diazinon and in rats preconditioned with 14 daily treatments at 10 mg/kg before the final administration of radiolabelled compound. The metabolite pattern was similar in the urine and faeces of the rats from all dose groups and from both sexes. The major urinary metabolites were identified as 2-isopropyl-6-methyl-4(1*H*)- pyrimidinone (average 38.2% of the totally applied dose), 2-(alpha-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (17.3%) and 2-(beta-hydroxyisopropyl-6-methyl-4(1*H*)-pyrimidinone (9.7%). Six unknown aqueous components accounted for an average of 14.9% of the administered dose, and trace amounts of unchanged diazinon (0.11%), diazoxon (0.14%) and the hydroxy-isopropyl derivative of diazinon (0.12%) were also detected. The identity of the metabolites was confirmed by gas chromatography and mass spectrometry (GC/MS) with synthetic standards.

6.2.1.3 Dogs

The urinary metabolites of Beagle dogs were characterized after oral administration of 4.0 mg/kg body weight ^{14}C-ring-labelled diazinon. The metabolite 2-isopropyl-4-methyl-6-hydroxypyrimidine accounted for 10% of the applied radioactivity in the urine and the tertiary hydroxy-isopropyl derivative of diazinon represented 23% (Iverson et al., 1975).

6.2.1.4 Sheep

When two sheep were dermally treated with [pyramidine-^{14}C]-diazinon, radiolabelled residues were detected in all tissues examined (heart, liver, kidney, back fat and leg muscle). Unmetabolized diazinon was the only significant residue in fat, and was a major residue in heart and leg muscle. The major metabolites in urine and all tissues except fat were 2-isopropyl-6-methyl-4(1*H*)-pyrimidinone (urine, 10% of the administered radioactivity; liver, 18%; kidney, 23%) and 2-(alpha-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (urine, 22.7%; liver, 10%; kidney, 28%), which were also present in the form of glucuronide conjugates. The identity of the metabolites was confirmed by GC/MS with synthetic standards. In addition, several unidentified

polar (urine, 18.6%) and minor amounts of non-polar (urine, 4.0%) metabolites were detected (Capps, 1990).

6.2.1.5 Goats

Two lactating goats were orally treated with [pyrimidine-^{14}C]-diazinon in gelatin capsules for four consecutive days. Similarly to sheep, in urine and faeces the metabolites 2-isopropyl-6-methyl-4(1*H*)-pyrimidinone (urine, 4.5% of the totally administered radioactivity; faeces, 2.6%) and 2-(alpha-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (urine, 12.5%; faeces, 1.7%) were identified. Approximately 48.6% of the urinary radioactivity consisted of unknown water-soluble compounds. Characterization of selected tissues showed the presence of mainly the above-mentioned metabolites. Unchanged diazinon, its hydroxy-isopropyl derivative and diazoxon accounted for less than 10% of the radioactivity detected in these tissues. Metabolites in fat consisted primarily of unchanged diazinon (66%), its hydroxy-isopropyl derivative (12.5%) and diazoxon (3%). The major metabolites in the milk were 2-isopropyl-6-methyl-4(1*H*)-pyrimidinone (39.3% of the residual radioactivity) and 2-(alpha-hydroxyisopropyl)-6-methyl-4(1*H*)-pirimidinone (37.3%). Substantial portions of the polar metabolites in urine, faeces and tissues were glucuronide conjugates. The identity of the metabolites was confirmed by GC/MS with synthetic standards (Simoneaux, 1988a,b,e).

6.2.1.6 Hens

Four laying Leghorn hens were treated with [pyrimidine-^{14}C]-diazinon in gelatin capsules for seven consecutive days at daily doses of 2.75 mg/kg day. The main metabolites detected in the excreta were unchanged diazinon (14.9% of the extractable radioactivity), 2-isopropyl-6-methyl-4(1*H*)-pyrimidinone (5.9%), 2-(alpha-hydroxy-isopropyl)-6-methyl-4(1*H*)-pyrimidinone (10.8%) and 2-(beta-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (7.2%). Approximately 25% of the radioactivity in the excreta consisted of unknown water-soluble compounds. The residues in tissues primarily consisted of 2-isopropyl-6-methyl-4(1*H*)-pyrimidinone (0.6-2.6% of the residual radioactivity), 2-(alpha-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (3.1-6.5%) and 2-(beta-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (2.0-5.7%). Unchanged diazinon was detected primarily in the peritoneal fat (2% of residues). In the eggs, primarily

2-isopropyl-6-methyl-4(1*H*)-pyrimidinone (yolk, 11.1% of the residual radioactivity; white, 9.4%), 2-(alpha-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (yolk, 18.6%; white, 33.3%) and 2-(beta-hydroxyisopropyl)-6-methyl-4(1*H*)-pyrimidinone (yolk, 7.0%; white, 35.3%) were detected. As in goats, a substantial portion of the polar metabolites in tissues, eggs and excreta were glucuronide conjugates. The identity of the metabolites was confirmed by GC/MS with synthetic standards (Simoneaux, 1988c,e; Simoneaux, 1989).

More information on kinetics and metabolism in other species is given in chapter 9.

6.2.2 In vitro *metabolic transformations*

The metabolism of [ethoxy-^{14}C]-diazinon and diazoxon was studied *in vitro* using rat liver cell fractions. It was shown that the degradation by diazinon is catalysed by a microsomal enzyme that requires NADPH and oxygen, and is inhibited by carbon monoxide. It is presumably the cytochrome P-450 oxidase system. Diazoxon was shown to be degraded by enzymes located in the nuclear, mitochondrial, microsomal and soluble fractions of the liver. The microsomal enzymes were the most active and were not dependent on NADPH. Reduced gluthation had little effect. With diazinon, products of the reactions were diethylphosphorothioic acid and diethylphosphoric acid. Diazoxon was degraded to diethylphosphoric acid (Yang et al., 1969, 1971; Nakatsugawa et al., 1969). These results were confirmed by independent experiments (Dahm, 1970). The oxidation of diazinon was investigated by using microsomal preparations from rat liver. The major metabolic products of diazinon were hydroxydiazinon, diazoxon and hydroxydiazoxon, which are biologically active, and additional inactive products such as diethylphosphorothioic acid, diethylphosophoric acid and derivatives of the pyrimidyl moiety. It was demonstrated that desulfuration, hydroxylation of the ring alkyl side-chain and cleavage of the aryl phosphate bond may occur, depending on the presence of NADPH or NADH. EDTA stimulated the overall metabolism of diazinon (Shishido et al., 1972a).

The enzymatic hydrolysis of diazoxon was investigated using rat tissue homogenates. The hydrolytic activity of the tissues decreased in the order liver>blood>lung>heart>kidney>brain. In the liver, the hydrolytic activity was localized in microsomal preparations. Diethyl phosphoric acid and 2-isopropyl-4-methyl-6-hydroxypyrimidine were

identified as the products. The reactions were inhibited by EDTA, heavy and rare earth metal ions, and sulfhydryl reagents (L-cysteine, 2-mercaptoethanol, thioglycolic acid), while calcium ions activated the hydrolysis (Shishido & Fukami, 1972).

Liver homogenates were prepared from male mice (North Carolina Department of Health strain) and incubated for 1 h with either ^{14}C-diazinon or ^{14}C-diazoxon. Inhibition of metabolism was studied by co-incubation with piperonyl butoxide, NIA 16824 or 1-(2-isopropylphenyl) imidazole. Diazoxon formation from diazinon (thiophosphate to phosphate conversion) was inhibited by 45 to 60% by the inhibitors studied. All the inhibitors also reduced oxidative dearylation of diazinon to diethyl phosphoric and diethyl phosphorothioic acids (Smith et al., 1974).

Conjugation with glutathione forms the third enzymatic mechanism of the diazinon metabolism in rat tissue preparations (liver, heart, brain, lung, kidney and blood were investigated). The highest activity (14-89 times as high as in other tissues) for this reaction was localized in the cytoplasmatic fractions of the liver. The reaction products were identified as diethyl phosphorothioic acid and S-(2-isopropyl-4-methyl-6-hydroxypyrimidinyl) glutathione, which were formed by conjugation and simultaneous cleavage of the phosphate ester bond. The enzymatic activity was increased by the addition of glutathione-SH, and was inhibited by various sulfhydryl reagents, oxidized glutathione and some chelating agents (*o*-phenanthroline, 8-hydroxyquinoline) (Shishido et al., 1972b).

6.3 Metabolic aspects of diazinon toxicity

Diazinon was incubated with liver microsomes and liver slices from sheep, cow, pig, guinea-pig, rat, turkey, chicken and ducks. Hydroxydiazinon, isohydroxydiazinon, dehydrodiazinon, their oxons and diazoxon were identified and determined quantitatively or semi-quantitatively. It was shown that yields and rates of production of the metabolites varied greatly between the species. The production of the oxon was not generally correlated with susceptibility to diazinon poisoning, although it was lowest in the least susceptible animal, the sheep. The highly susceptible avian species (acute oral LD_{50} of around 2-15 mg/kg) do not produce higher rates of oxons than rat or pig (acute oral LD_{50} around 300-600 mg/kg). However, the mammalian

blood hydrolyses diazoxon rapidly, whereas the avian species have virtually no hydrolytic activity. It was concluded that extrahepatic metabolism of diazinon, in particular the hydrolysis of diazoxon in the blood, appears to be the main factor affecting susceptibility to diazinon poisoning. In mammals the extrahepatic metabolism of diazinon is more important toxicologically than the metabolism in the liver, while the liver is probably the most important site of metabolism in avian species (Machin et al., 1975).

Recently, the hydrolytic metabolism of diazinon by plasma was investigated in 92 individuals of Hispanic origin (Davies et al., 1996). Diazoxon is hydrolysed by the enzyme paraoxonase (PON1), leading to the formation of 2-isopropyl-4-methyl-6-hydroxypyrimidine and diethylphosphate. An important observation of this study was that the effect of the PON1 polymorphism for diazoxon hydrolysis relative to paraoxon hydrolysis was reversed. Thus, RR individuals (Arg192 homozygotes) who displayed high paraoxonase activity had lower diazonoxonase activity (mean = 7948 U/litre) than QQ homozygotes (12 318 U/litre).

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

7.1 Single exposure

7.1.1 Oral

Improvements since 1979 in the manufacturing of diazinon have significantly reduced the content of highly toxic by-products, in particular tetraethyl-pyrophosphate (TEPP). As a result of these stepwise improvements, the acute oral LD_{50} of technical grade diazinon increased to values around 1000 mg/kg (Piccirillo, 1978; Bathe & Gfeller, 1980; Schoch & Gfeller, 1985; Kuhn, 1989a). The most recent study resulted in an oral LD_{50} in rats of 1250 mg/kg. The LD_{50} values for different species are summarized in Table 2.

Signs of poisoning after a single dose of diazinon are typical of organophosphate intoxication and include decrease of spontaneous activity, sedation, dyspnoea, ataxia, tremors, muscle spasms, convulsions, lacrimation and diarrhoea. The signs were found to be reversible in surviving animals.

Diazinon (88% purity) was administered by gavage to 15 rats per sex and dose at single doses of 0, 2.5, 150, 300 and 600 mg/kg (Potrepka, 1994). Three, 9 or 24 h after dosing, five animals of each group were bled for determination of serum and red blood cell cholinesterase activity and then killed for determination of CNS cholinesterase activity. There was no mortality. Signs of cholinergic poisoning, e.g., salivation, diarrhoea and muscle fasciculations, were observed in animals of both sexes dosed at 300 and 600 mg/kg. Clinical signs first appeared 3 h after treatment. Maximum observable toxicity was noted 9 h after treatment in males and 24 h after treatment in females. Serum cholinesterase activity was significantly decreased at all time points in all groups treated with 2.5 mg/kg or more. Maximum inhibition was observed 9 h after dosing, and values remained depressed at 24 h after dosing. Red blood cell cholinesterase activity was significantly inhibited at all time intervals in animals of both sexes treated with ≥150 mg/kg. Again, maximum inhibition was observed 9 h after dosing, and activity remained depressed at 24 h after dosing. In addition, a significant inhibition of red blood cell

Table 2. Acute toxicity of diazinon[a]

Species	Sex	Route of administration	LD_{50} (mg/kg)	Reference
Rat	male	oral	235	Gasser (1953)
Rat	male	oral	435	Shaffer & West (1960)
Rat	male	oral	250	Gaines (1969)
Rat	female	oral	285	Gaines (1969)
Rat	both	oral	300	Piccirillo (1978)
Rat	both	oral	422	Bathe & Gfeller (1980)
Rat	both	oral	1012	Schoch & Gfeller (1985)
Rat	both	oral	1250	Kuhn (1989a)
Rat	male	dermal	900	Gaines (1960)
Rat	female	dermal	455	Gaines (1960)
Rat	both	dermal	>2150	Bathe (1972a)
Rat	both	inhalation	>2300[b]	Holbert (1989)
Mouse	male	oral	82	Bruce et al. (1955)
Mouse	both	oral	96	Gasser (1953)
Mouse	both	oral	187	Bathe (1972b)

Table 2 (contd).

Mouse	both	i.p.	65	Klotzsche (1955)
Guinea-pig		oral	320	Gasser (1953)
Rabbit		oral	130	Gasser (1953)
Rabbit	both	dermal	>2020	Kuhn (1989b)
Turkey		oral	6.8	FAO/WHO (1965)
Chicken		oral	40.8	FAO/WHO (1965)
Goose		oral	14.7	FAO/WHO (1965)
Gosling		oral	2.8	Egyed et al. (1974)

[a] It should be noted that progressive improvement in the manufacturing process has reduced the acute toxicity of diazinon.
[b] This value is the LC_{50}, the units being mg/m^3.

cholinesterase activity was noted in females dosed with 2.5 mg/kg diazinon 9 h after dosing. Cerebellum, cerebral cortex, striatum, hippocampus and thoracic spinal cord cholinesterase activities were decreased in female rats dosed with ≥150 mg/kg at all three time points. Cerebellum, striatum and hippocampus cholinesterase activities were decreased in male rats dosed with ≥150 mg/kg at all three time intervals, whereas cerebral cortex and thoracic spinal cord cholinesterase activities were decreased in male rats dosed with ≥150 mg/kg at 9 and 24 h after dosing. The NOAEL for inhibition of brain cholinesterase activity was 2.5 mg/kg for both sexes (Potrepka, 1994).

Brain cholinesterase activities were determined for white-footed mice (*Peromyscus leucopus*) orally dosed with diazinon at 18.8 mg/kg body weight (Montz & Kirkpatrick, 1985). Following treatment with diazinon, a latent period of approximately 6 h elapsed during which time acetylcholinesterase activity was relatively unaffected. After the latent phase, ChE activity rapidly declined to a minimum 12 h after dosing. After 48 h, ChE activity recovered to a level only slightly below that of the controls. The response of both male and female mouse brain ChE activities declined rapidly at 6 h and reached a minimum 24 h after dosing. ChE activity of treated animals was comparable to that of controls 48 h after treatment. Brain ChE activities of treated female mice were significantly lower ($P < 0.05$) than those of treated males.

An acute oral toxicity study in rats was conduced in two phases to determine a NOEL of the test material (87.9% active ingredient) for clinical, behavioural and body weight effects in phase 1 and a NOEL for effects on plasma, red blood cell and brain cholinesterase in phase 2 after single oral gavage application to rats. In phase 1 each test group consisted of 5 rats. The applied dose levels were 25 and 50 mg/kg body weight for female rats only; levels of 100, 250 and 500 mg/kg body weight were tested in both sexes. One female given 500 mg/kg body weight died. Clinical signs such as miosis, hypoactivity, absence of pain reflex, red-stained face, yellow-stained abdomen/ urogenital area, soft stool or few faeces were seen in all animals except 100-mg/kg males and 25-mg/kg females. The NOAEL for clinical/ behavioural/body weight effects was 100 mg/kg body weight in males and 25 mg/kg body weight in females. In phase 2 each test group consisted of 5 rats. Males were treated with 0.05, 0.50. 1.0, 10.0, 100 or 500 mg/kg body weight and females with 0.05, 0.12, 0.25, 2.5, 25 and 250 mg/kg body weight. Clinical signs such as miosis, hypo-

activity, absence of pain reflexes, staggered gait, excessive salivation, red-stained face and yellow-stained and/or wet ventral/urogenital area were only observed in males at 500 mg/kg body weight (one male at 100 mg/kg body weight showed miosis) and females at 250 mg/kg body weight The only findings at necropsy were yellow staining of the perineum and red paranasal discharge in animals of these dose groups. Plasma cholinesterase activity was significantly reduced in males dosed with 10, 100 or 500 mg/kg body weight and in females dosed with 2.5, 25 or 250 mg/kg body weight. Red blood cell cholinesterase activity was significantly lower in males given 100 or 500 mg/kg body weight and in females given 25 or 250 mg/kg body weight. Brain cholinesterase activity was significantly reduced at the highest dose level for both sexes. Brain cholinesterase activity in females dosed with 25 mg/kg body weight was inhibited by 37% (without reaching statistical significance) (Glaza, 1993).

7.1.2 Dermal

Diazinon was dispersed on the shaved back of each of three male and three female Tif: RAI rats at a level of 2150 mg/kg and covered with aluminium foil for 24 h. None of the animals died. Neither clinical signs nor dermal irritation was observed. Autopsy revealed no substance-related gross organ changes. The acute dermal LD_{50} in rats was found to be greater than 2150 mg/kg (Bathe, 1972a). Sherman strain rats were given one dermal application of diazinon dissolved in xylene, and no attempt was made to remove the compound during the observation time of 14 days. The LD_{50} was 900 mg/kg for males and 455 mg/kg for females (Gaines, 1960).

Dermal LD_{50} values for diazinon were determined in mice after application of the solution to hind feet. Values were simultaneously generated for the ED_{50} for both cholinesterases (acetylcholinesterase and pseudocholinesterase). LD_{50} values were higher than those reported for mice treated on shaved back skin. Diazinon appeared to have much more inhibitory potential for blood than for nervous tissue cholinesterase (Skinner & Kilgore, 1982).

Undiluted diazinon was applied to the clipped dorsal trunk of each of five male and five female New Zealand White rabbits at a level of 2020 mg/kg and kept under semi-occlusive dressing for 24 h. Signs were typical of organophosphate intoxication; two out of ten animals died. The LD_{50} was >2020 mg/kg (Kuhn, 1989b,c).

7.1.3 Inhalation

Sprague-Dawley rats were exposed (whole body exposure) to diazinon for 4 h. The acute inhalation LC_{50} for diazinon MG 8 FL880045 was greater than 2330 mg/m^3 when it was administered undiluted as an aerosol (Holbert, 1989).

Groups of five male and five female HSD:SD rats were exposed to an aerosol generated from undiluted liquid diazinon MG87% (88% purity) for 4 h (nose-only exposure). An exposure concentration of 5540 mg/m^3 was obtained, 8.82% of particles being smaller than 1 mm in diameter. There was no mortality. Prominent in-life observations included activity decrease, piloerection and polyuria, no longer seen by day 6. Body weight gain was largely unaffected. Gross necropsy revealed discoloration of the lungs in all animals. The acute inhalation LC_{50} for diazinon in the rat was greater than 5440 mg/m^3 (Holbert, 1994).

7.1.4 Intraperitoneal

Mild structural and functional changes were observed in the liver and testes of rats after a single intraperitoneal administration of diazinon (21.6 mg/kg). Kidney, however, showed no pathological lesions. Attempts were made to correlate the pathological changes in these organs with the activity of succinic dehydrogenase, adenosine triphosphatase and alkaline phosphatase (Dikshith et al., 1975). A single intraperitoneal dose of diazinon caused hyperglycaemia in rats, which peaked 2 h after intraperitoneal treatment with 40 mg diazinon/kg. The brain acetylcholinesterase activity was significantly reduced. The blood level of pyruvic acid was unchanged while that of lactic acid was significantly increased. In diazinon-treated hyperglycaemic animals, the glycogen content of the brain was depleted, the activities of glycogen phosphorylase, phosphoglucomutase and hexokinase were significantly increased, and the activity of glucose-6-phosphatase remained unchanged. Lactate dehydrogenase activity was increased by treatment with diazinon. The induced changes may have compensated for the energy requirement of stimulatory effects caused by the pesticide (Husain & Matin, 1986; Matin & Husain, 1987; Matin et al.,1989). Changes in energy metabolism are regarded as secondary, following cholinesterase inhibition.

In an acute intraperitoneal study in rats, an LD_{50} value of 260 mg/kg body weight was determined for both sexes. Clinical signs were typical of organophosphate poisoning, e.g., sedation, dyspnoea and tonic-clonic spasms. Surviving animals had recovered within 3 to 6 days, and no substance-related gross organ changes were observed (Bathe, 1973).

Diazinon given as an intraperitoneal single dose (40 mg/kg) to rats produced tremors and convulsions with lactic acidosis. This was accompanied by depletion of glycogen phosphorylase activity in the triceps and diaphragm muscles 2 h after the administration (Husain & Matin, 1986; Husain & Ansari, 1988).

7.2 Short-term exposure

7.2.1 Oral

7.2.1.1 Rats

Davies & Holub (1980a,b) found that diazinon (99.2% purity) fed to rats for 4 weeks at doses up to 25 mg/kg diet produced no visible toxic manifestations such as tremors or hyperexcitability. Feeding diazinon 25 mg/kg diet for 30 days produced more significant reduction of cholinesterase activity in plasma (by 22-30%) and brain (by 5-9%) among treated females than among males. Erythrocyte acetylcholinesterase activity was significantly more depressed (by 13-17%) in treated females than in males at days 21-28 of the feeding trial. The greater degree of cholinesterase inhibition in females was possibly attributable to the higher amount of diazinon ingested by females than by males after day 15 of the study.

Female Wistar rats were fed a semi-purified diet containing either no pesticide or 0.1 to 15 mg/kg diazinon for up to 92 days. At specified times, blood samples were taken to measure plasma and erythrocyte cholinesterase activity using a radiometric method. Additional rats were killed to determine brain cholinesterase activity. Measurements included body weight gain and feed consumption during the growing period. Feeding diazinon at the stated levels produced no visible toxic manifestations. Treated animals showed weight gain and feed consumption that was comparable to controls. Feeding trials lasting up to 90 days revealed that rats were highly sensitive to diazinon after 31 to 35 days exposure, as judged by

reduction of plasma and erythrocyte cholinesterase activities. Brain acetylcholinesterase was found to be practically insensitive to dietary intake of diazinon (1.0 to 15 mg/kg), although moderate reduction (by 6%) of brain enzyme activity was noted among animals fed 10 mg/kg diet at day 92. For all feeding trials, plasma cholinesterase was a more sensitive indicator of diazinon exposure than erythrocyte or brain acetylcholinesterase. The NOAEL of diazinon for the rat was estimated to be 0.1 mg/kg diet, which is equivalent to a daily intake of 0.009 mg/kg body weight per day (Davies & Holub, 1980a).

In a feeding study, diazinon (87.7% pure) was administered to groups of 15 male and 15 female Sprague Dawley rats for 13 weeks at dietary concentrations of 0, 0.5, 5, 250 and 2500 mg/kg, corresponding to mean daily doses of 0, 0.03, 0.3, 15 and 168 mg/kg body weight in males and 0, 0.04, 0.4, 19 and 212 mg/kg body weight in females, respectively. The rats treated at the highest dose level showed hypersensitivity to touch and sound and some of the males showed apparent aggressiveness, hyperactivity and soft faeces. Body weight gain and food consumption were reduced in both sexes. At this dose level, the haematological examination revealed a decreased haemoglobin level, a lower haematocrit and an increased number of reticulocytes in the females. The examination of blood biochemistry revealed a reduced activity of serum cholinesterase in both sexes treated with 5 mg/kg diet or more. In addition, the low-dose females showed a 17% reduction in the erythrocyte cholinesterase activity. At 250 mg/kg diet or more, the erythrocyte and brain cholinesterase activities were reduced in both sexes. The absolute and relative liver weights were increased in both sexes in the highest dose level, and there was microscopic evidence of centrilobular hepatocellular hypertrophy (Singh et al., 1988). The NOAEL, based on reduction in brain cholinesterase activity, was 5 mg/kg diet (equivalent to 0.4 mg/kg body weight per day).

In a second, similar, study (Pettersen & Morrissey, 1994), Sprague Dawley rats were fed diazinon at 0, 0.3, 30, 300 or 3000 mg/kg diet for 13 weeks. Serum, erythrocyte and regional brain cholinesterase inhibition was measured in groups of five males and five females at weeks 4, 8 and 13. Serum and erythrocyte cholinesterases were inhibited by 45-86 and 60-75%, respectively, at 30 mg/kg diet, but not consistently at 0.3 mg/kg diet. Brain regional cholinesterase was inhibited by up to 25% in females at 30 mg/kg diet and by 55-75% at 300 mg/kg diet. Males were less sensitive, showing

no effect at 30 mg/kg diet and a fall of 62-77% at 3000 mg/kg diet. Observable neuromuscular deficits were seen only at 3000 mg/kg diet. Consequently the NOEL and NOAEL for this study was 0.3 mg/kg diet (equivalent to 0.019 mg/kg body weight per day), based on the reductions in serum, erythrocyte and brain cholinesterase seen at the next highest dose of 30 mg/kg diet. However, given the lack of an intermediate dietary level of 5 mg/kg, which set the NOAEL in the Singh et al. (1988) study, and the modest fall in brain cholinesterase seen at 30 mg/kg diet in this second study, it is concluded that the previous NOAEL of 5 mg/kg diet (0.4 mg/kg body weight per day) should stand.

The effect of low levels of diazinon treatment on four marker enzymes in rat heart and skeletal muscles have been investigated by Wilkinson et al. (1986). Typical differences in succinate dehydrogenase (SDH), lactate dehydrogenase (LDH), phosphofructokinase (PFK) and hexokinase (HK) activities were observed between heart and skeletal muscles. Diazinon feeding had no effect on heart, soleus, gastrocnemius and plantaris SDH, LDH or PKF enzyme activities after 28 weeks. HK activity was significantly increased in sham-control soleus and plantaris muscle after 28 weeks. Diazinon feeding inhibited HK activity in plantaris muscle after 28 weeks treatment. These results demonstrate that chronic low levels of diazinon have little effect on the glycolytic and oxidative activity in heart and skeletal muscles.

Adult Wistar rats were given diazinon by gavage twice weekly at a dose of 0.5 mg/kg body weight for twenty-eight weeks. Selected control and experimental animals were killed after 7, 14 and 28 weeks. Histological examination of the liver revealed that animals repeatedly treated with sublethal doses of diazinon sustain a form of hepatic injury characterized by cellular lipid accumulation. The finding of increased lipid accumulation in the liver following prolonged treatment with diazinon, however, still does not resolve the question of whether impaired lipid metabolism and/or storage is the primary effect (Anthony et al., 1986).

Rats were exposed to diazinon-impregnated strips in a conventional laboratory animal room. The air in the room was monitored for the pesticide. Erythrocyte and plasma cholinesterase activities were determined periodically. Air concentration of the pesticide never exceeded 1.34 mg/m^3. No significant change in enzyme activities were observed (Hinkle et al., 1980).

7.2.1.2 Dogs

Feeding studies with dogs (Bruce et al., 1955; Williams et al., 1959) did not differentiate between the sexes and therefore relevant data from male and female animals were pooled. In another study (Barnes et al., 1988) diazinon (87% pure) was given to groups of four male and four female Beagle dogs for 13 weeks at concentrations of 0, 0.1, 0.5, 150 and 300 mg/kg diet, corresponding approximately to a mean daily intake of 0.0034, 0.02, 5.9 and 10.9 mg/kg body weight respectively. Vomiting was observed in groups fed a diet containing 150 or 300 mg/kg. Serum cholinesterase activity was reduced at 0.5 mg/kg or more in males and at 150 and 300 mg/kg in females. Erythrocyte and brain cholinesterases activity was depressed at 150 and 300 mg/kg in both sexes. The histopathological examination revealed a moderate atrophy of pancreatic acini in one high-dose group of male dogs. Body weight gain was decreased in females at 150 mg/kg diet and in both sexes at 300 mg/kg diet. The serum calcium level was decreased in females at 150 mg/kg diet and in males at 150 and 300 mg/kg diet. The serum albumin level was decreased in both sexes at 300 mg/kg diet. As a slight reduction of serum cholinesterase activity was the only change observed, 0.5 mg/kg diet, corresponding to a mean diazinon intake of 0.02 mg/kg body weight per day, is considered to be the dietary concentration causing no toxicological effect (NOAEL), based on inhibition of brain and erythrocyte cholinesterase at higher doses.

7.2.1.3 Pigs

Pigs were orally administered diazinon in capsules at doses of 0, 1.25, 2.5, 5 and 10 mg/kg body weight daily for periods of up to 8 months. In pigs, mortality and cholinergic signs of poisoning were evident at 2.5 mg/kg body weight per day (FAO/WHO, 1979).

7.2.2 Inhalation

Two short-term inhalation studies were conducted in rats. In the first study, diazinon (97.1% pure) was administered in an inhalation chamber to four groups of nine male and female Tif RAIf rats for 6 h per day, 5 days a week, for three weeks, at concentrations of 0, 151, 245 and 559 mg/m^3. Four animals of each sex from the control group and from the highest concentration group were kept for a 25-day post-treatment observation period, while the others were sacrificed at day

21 after treatment. No compound-related deaths occurred. Exophthalmus and diarrhoea were observed at all dose levels. In addition, the high-dose group animals showed salivation, ruffled fur and tonic-clonic convulsions during 2 h after each exposure. No toxic signs occurred in the 25-day follow-up period. Food consumption was reduced during the first three days of exposure in the high-dose group, plasma cholinesterase activity was reduced in the intermediate and high-dose groups, and brain cholinesterase activity was reduced at all dose levels. Erythrocyte cholinesterase activity was reduced in the high-dose group. The changes were reversible. There were no macro or histopathological findings related to the exposure to diazinon (Zak et al., 1973).

In the second study the main purpose was the definition of a NOAEL for cholinesterase inhibition. Groups of ten male and ten female Tif RAlf rats were exposed to diazinon 6 h a day for 5 days per week for 3 weeks. The effective concentrations at the inhalation site were 0, 0.05, 0.46, 1.57 and 11.6 mg/m^3 air. There were no compound-related signs, and no changes in body weight or food consumption. In comparison with the control animals, the number of erythrocytes, haemoglobin level and packed cell volume were slightly lower in the highest-dose group. A minor decrease of brain cholinesterase activity was noted in the highest-dose group of females. Plasma glucose levels were significantly reduced among males exposed to 1.57 and 11.6 mg/m^3 (Hartmann, 1990). As the exposure to 0.46 mg/m^3 inhibited the plasma cholinesterase only, this concentration is the NOAEL.

7.2.3 Dermal

7.2.3.1 Rabbits

Diazinon (97.1% pure) was suspended in 50% aqueous polyethylene glycol 300 and topically administered under semi-occlusive dressing to groups of five male and five female albino rabbits at daily doses of 0, 1, 5 and 100 mg/kg body weight for 5 days per week for 3 weeks. In the highest-dose group, four males treated at 100 mg/kg died during the first week of treatment. Consequently, the dose was reduced to 50 mg/kg. Clinical signs were observed in the highest-dose group and included anorexia, ataxia, fasciculations, tremors, diarrhoea, hypoactivity, hypotonia and salivation. Most of the signs disappeared after the dose was reduced. Mild dermal reactions

were noted at site of test substance administration. Body weight gain and food consumption was similar in all groups, and most laboratory parameters remained unaffected by the treatment. Reduced cholinesterase activities were found in serum, red blood cells and the brain in animals treated at ≥5 mg/kg. In the highest-dose group, the reductions were significant for brain, red blood cells and serum cholinesterase activities, while with 5 mg/kg there was a statistically significant decrease of activity in the brain cholinesterase of females only. In the highest-dose animals, the histopathological examination showed a slight hyperkeratosis of the skin at the site of treatment (Tai & Katz, 1984). The NOEL was considered to be 1 mg/kg, based on inhibition of brain cholinesterase.

7.3 Long-term exposure

7.3.1 Rats

Groups of 30 or 40 Sprague Dawley male and female rats received diazinon (87.7% pure) at dietary concentrations of 0, 0.1, 1.5, 125 and 250 mg/kg (equivalent to a mean daily diazinon intake of 0, 0.004, 0.06, 5 and 10 mg/kg body weight in males and of 0.005, 0.07, 6 and 12 mg/kg body weight in females) for 99 weeks. An additional control group received 26.5 mg/kg diet epoxidized soybean oil, the stabilizer used in technical diazinon, at the concentration corresponding to the application to the test group of animals. Eight to ten randomly selected animals per sex and dose group were killed after one year of treatment, and nine or ten animals from the control group and from the highest-dose group were killed after 4 weeks of recovery at week 56. There were no compound-related clinical signs. At 250 mg/kg diet, the mean body weight and the food consumption were slightly, but significantly, increased in both sexes. Serum cholinesterase activities were reduced at ≥1.5 mg/kg diet. Red blood cell and brain cholinesterase activities were inhibited in groups fed on a diet containing 125 or 250 mg/kg. Cholinesterase inhibition was at least partially reversible during the 4-week recovery period after one year of treatment. No treatment-related changes were seen during pathology or histology examination (Kirchner et al., 1991). A pathological re-evaluation of eyes and optic nerves from all control and high-dose animals of the above study from interim necropsy (week 52), interim recovery necropsy (week 56) and chronic necropsy (week 98/99) was conducted. Histopathological lesions like cataracts, inflammatory changes of the globe and surface of the eye and several

different types of retinal atrophy were found in both control and treated animals at final sacrifice. None of these findings had an increased incidence in treated rats compared to controls and they were not regarded as compound-related. As the dietary concentration of 1.5 mg diazinon/kg, equivalent to a mean intake of 0.06 mg/kg body weight per day, inhibited serum cholinesterase only, this dose level was considered to be the NOAEL (Mann, 1993).

7.3.2 Dogs

Groups of Beagle dogs (four males, four females) received diazinon (87.7% pure) for 52 weeks at dietary concentrations of 0, 0.1, 0.5, 150 and 300 mg/kg (equivalent to a mean daily intake of 0.0032, 0.015, 4.7 and 7.7 mg/kg body weight for males and 0.0037, 0.02, 4.5 and 9.1 mg/kg body weight for females). Owing to a general lack of body weight gain, the highest dose level was reduced from 300 mg/kg diet to 225 mg/kg diet after 14 weeks of treatment. One male dog from the highest-dose group showed emaciation and dehydration due to severely reduced food consumption and weight reduction. In the other animals from the highest-dose group (300 mg/kg/diet) the body weight gain was also severely depressed during the initial 14 weeks of treatment. After the reduction of dose to 225 mg/kg/diet, body weight gain remained depressed in two of the males, while the females returned to normal. A slightly reduced body weight gain was also noted among males at 150 mg/kg diet. Food consumption was reduced in both sexes fed on a diet containing ≥150 mg/kg diazinon. Haematology and urine analysis showed no treatment-related changes. Significantly decreased cholinesterase activities were noted at ≥0.5 mg/kg diet. Serum cholinesterase activity was inhibited at 150 mg/kg diet at all sampling intervals and at several occasions at 0.5 mg/kg diet. Red blood cell and brain cholinesterase activities were reduced at ≥150 mg/kg diet. In addition, a slight reduction in the mean serum amylase activity was noted in both sexes fed a diet of ≥150 mg/kg. The organ weight analysis showed no treatment-related changes and macro- and histopathology were unremarkable (Rudzki et al., 1991). A re-evaluation of eyes and optic nerves from all control and high-dose animals from the study was conducted. No histopathological findings in the eyes were noted (Mann, 1993). The dietary diazinon concentration of 0.5 mg/kg, equivalent to a mean daily diazinon intake of 0.015 mg/kg, inhibited serum cholinesterase activity only, and was considered to be the NOAEL, based on inhibition of brain and erythrocyte cholinesterase.

7.3.3 Rhesus monkeys

This study was conducted with a 50% WP diazinon formulation containing an actual concentration of 48.6% diazinon. The dose levels given below refer to the active ingredient. Groups of three male and three female Rhesus monkeys received initial daily doses of 0, 0.1, 1.0 and 10.0 mg diazinon/kg body weight, administered by gastric intubation. After 34 days the doses were lowered to 0.05, 0.5 and 5.0 mg/kg and after 106 weeks of treatment the study was terminated.

Mortality was similar in all dose groups: the death of one animal at each dose was of infectious etiology. Clinical signs included tremor in the highest-dose group animals and an increased incidence of soft stools was noted at 1.0 and 10.0 mg/kg. In comparison to the controls, all treated animals gained slightly less weight. Treatment-related deviations in the laboratory parameters examined were limited to reductions of cholinesterase activities. At the 0.5 mg/kg dose level, the erythrocyte cholinesterase activity was occasionally reduced in some animals and plasma cholinesterase activity was consistently depressed. At the highest-dose level, plasma and erythrocyte cholinesterase activities were markedly inhibited and the brain cholinesterase activity was reduced in one monkey. The postmortem examinations revealed no changes of toxicological relevance. The daily dose of 0.5 mg diazinon/kg inhibited plasma and (occasionally slightly) erythrocyte cholinesterase activity. The toxicologically relevant brain cholinesterase activity remained unaffected. Therefore, this dose level was considered to be the NOAEL, based on inhibition of erythrocyte cholinesterase (Cockrell et al., 1966).

7.4 Skin and eye irritation; sensitization

7.4.1 Primary skin irritation

Diazinon (0.5 ml undiluted, technical material) was applied to the shaved skin of three male and three female New Zealand white rabbits and covered with gauze patches and an impermeable material. The dressing was removed after 4 h. Slight erythema and minimal oedema were seen in all rabbits, which disappeared within 1 week. In the report the compound received the descriptive rating as "slightly irritant" to rabbit skin (Kuhn, 1989b,c).

7.4.2 Primary eye irritation

Diazinon (0.1 ml undiluted technical material) was instilled into the conjunctival sac of three male and three female New Zealand white rabbits. In three additional female rabbits, the treated eyes were washed for 1½ min after the instillation of diazinon. Diazinon produced mildly irritating reactions of the conjunctivae, which disappeared within 72 h. It was rated as minimally irritating in washed and unwashed eyes of rabbits (Kuhn, 1989d).

7.4.3 Skin sensitization

Diazinon was examined for skin sensitizing effects in 10 Hartley Albino guinea-pigs. Ten animals were initially treated with 0.5 ml undiluted technical diazinon, applied to the shaved skin under semi-occlusive dressing for 6 h. After the third treatment one animal died, most probably due to intoxication. Therefore, further treatments were conducted with a 10% solution of diazinon in ethanol. After 11 treatments during the 3-week induction period and a 2-week rest phase, no sensitization resulted after a single challenge administration (Kuhn, 1989e).

7.5 Reproduction, embryotoxicity and teratogenicity

7.5.1 Reproduction

7.5.1.1 Rat

Diazinon (94.9% pure) was administered in the feed to groups of 30 male and 30 female Sprague Dawley rats for 10 weeks prior to mating, throughout mating of the F_0 animals and during two generations up to weaning and sacrifice of the F_2 pups. The dietary concentrations used were 0, 10, 100 and 500 mg/kg. Compound-related clinical signs and mortalities were limited to a few parental females treated with 500 mg/kg diet. The food consumption was generally comparable to, or slightly higher than, control values for females of both parental generations in the diazinon-treated groups, while the F_0 males showed a decreased food consumption during the premating period at both 100 and 500 mg/kg diet. The body weight increase was reduced at 500 mg/kg in the F_0 females and at 100 and 500 mg/kg for the F_1 animals of both sexes. There were no remarkable gross or microscopic findings or effects on organ weights in either the

F_0 or F_1 generation. Reproductive parameters including precoital interval, gestation duration, mating, fertility and pregnancy indices were unaffected by the treatment in both generations at the dose levels of 10 and 100 mg/kg diet. At 500 mg/kg there was an increase in the proportion of dams with prolonged gestation in both generations, and in the F_1 animals there was a trend toward a decrease in the number of pregnancies and viable newborns and adverse effects on fertility indices. Mating behaviour was unaffected by treatment. Litter size on lactation day 0 was decreased in both the F_1 and F_2 pups at 500 mg/kg, whereas pup weight and sex ratio on day 0 were comparable to controls for both generations. Decreases in pup survival and corresponding decreases in pup weight were observed in both generations at 500 mg/kg and in the F_1 pups at 100 mg/kg. Compound-related clinical and necropsy observations were noted in some F_1 pups at 500 mg/kg (tremor, no milk in stomach). NOAEL was 10 mg/kg diet for pups and parental animals (Giknis, 1989).

7.5.1.2 *Cattle*

As a part of a survey to determine causes of abortion in Wisconsin dairy cattle, the possible role of pesticides was examined. Of 31 aborted fetuses examined, none contained traces of diazinon. Two gravid, non-lactating Holstein Friesian cows were orally treated in their feed with diazinon (Diazinon W 50 wettable powder formulation) at daily doses of 6.6 mg/kg body weight during their second semester of gestation until term. The calves were killed after parturition and samples of perirenal fat, liver and kidney were investigated for residues of diazinon, as were samples of colostral milk from the cows. A histopathological examination of the calves, livers and kidneys was conducted. Both cows treated with diazinon vomited and refused feed on day 20 of treatment. No abortions occurred and no gross or histopathological changes were found in the calves. No diazinon residues were detected in the tissues investigated or in the milk (Macklin & Ribelin, 1971).

7.5.2 *Embryotoxicity and teratogenicity*

7.5.2.1 *Mice*

Groups of 19-22 mated female F_2 hybrid mice were orally treated with diazinon (admixed to peanut butter, purity not specified) at daily doses of 0, 0.18 and 9 mg/kg body weight from the day of mating until

delivery. The dams were weighed daily. After delivery, the physiological and behavioural development of the pups was examined. Mothers of all groups gave birth to viable offspring. Litter size and the birth weights of the pups were similar in treated and untreated groups. In the group receiving the higher dose of diazinon, the body weight development of pups was depressed during their first postnatal week. According to the authors, the testing of physiological and behavioural development revealed subtle deviations from the normal development in the offspring from the treated females. After sacrifice at 101 days of age, the brains of the offspring of mothers treated at the high-dose level showed ambiguous neuropathological changes in the forebrains (Spyker & Avery, 1977). This study raises questions that cannot be answered from the data presented.

7.5.2.2 *Rats*

Diazinon (purity 95%) was administered orally by gavage to groups of 28 to 30 pregnant Sprague-Dawley-derived rats on days 6 to 15 of gestation at dose levels of 0, 15, 50 and 100 mg/kg body weight On day 21 of gestation, all dams were killed and the fetuses delivered by cesarean section. The dams of the 100 mg/kg group reacted to the treatment by a marked decrease in food consumption and a body weight loss in the early administration phase. The dams of the 15 and 50 mg/kg group showed no reaction. The parameters of reproduction (number of corpora lutea, implantations, resorptions, fetal deaths and viable fetuses) showed no treatment-related intergroup differences. The fetal body weights were similar in all groups and the examination of the offspring did not reveal any teratogenic effects of the treatment. The NOAEL was 50 mg/kg body weight (Fritz, 1974).

In rats, doses (95.2 mg/kg body weight on day 9) that increased maternal mortality reduced fetal development, as indicated by reduced weight of litters and mild "hydronephrosis", but caused no real teratogenic effect (Dobbins, 1967). A similar result was reported for an intraperitoneal dosage of 100 and 150 mg/kg on day 11 (Kimbrough & Gaines, 1968). Repeated administration (40, 50 or 60 mg/kg body weight per day) on days 7 to 19 of gestation reduced the growth of the dams but had no effect on the number of resorptions or corpora lutea, on litter size, or on fetal weight. The cholinesterase activity of the fetal brain was reduced. A dosage of 75 mg/kg body weight per day was fatal to dams in 4 to 5 days (Hoberman et al., 1979).

Diazinon (97.4% pure) was administered by gavage to groups of 21 to 25 pregnant Sprague-Dawley rats from day 6 to 15 of gestation at dose levels of 0, 10, 20 and 100 mg/kg body weight. On day 20 of gestation, all dams were killed and the fetuses delivered by cesarean section. In the highest-dose group of, dams a decreased food consumption was noted during days 6-9 of gestation and the animals lost weight. The body weight gain of the dams showed some recovery thereafter, but the overall body weight gain of the highest-dose group remained significantly below that of the untreated controls. The numbers of corpora lutea and implantations were similar in all groups. Resorptions were significantly increased only in the top-dose group and, accordingly, the number of live fetuses was decreased. The fetal body weights were higher in the top-dose group than in the untreated controls. Three single instances of external malformations were observed at the highest-dose level (one fetus with a filamentous tail, one fetus with umbilical hernia and one fetus with sublingual extraneous soft tissue). Since the malformations were not morphologically related, they were considered to be secondary to maternal toxicity. An increased incidence of rudimentary 14th ribs was noted in the fetuses of the highest-dose group, although it remained within the limits of historical controls. The finding was considered to be related to fetotoxicity, secondary to severe maternal toxicity. Other fetal anomalies were comparable between treated and untreated groups. No evidence of teratogenic effect of diazinon was found (Infurna & Arthur, 1985).

7.5.2.3 *Hamsters*

In Golden Syrian hamsters diazinon was administered as individual oral doses (0.125 and 0.25 mg/kg body weight) during the period of organogenesis. Technical grade diazinon diluted with corn oil was used. The dose volume was 10 ml/kg body weight. Control animals received corn oil on the same days of gestation. The hamsters were killed on day 14 of gestation. All fetuses were examined for gross defects when delivered by cesarean section. The viability of hamster fetuses delivered on day 15 was checked by placing them in a chicken hatching incubator for 6 h. All fetuses with enough developmental form for determination of structural defects were counted in determining the number of fetuses per litter. The total number of fetuses in each treatment group was divided by the number of mothers surviving to term. Fetuses dying in late embryonic life and resorption sites were counted as dead fetuses. No bone defects were

seen in four fetuses chosen at random from each litter for staining and examination of skeleton. Diazinon did not produce any terata when administered to hamsters (Robens, 1969).

7.5.2.4 *Rabbits*

Robens (1969) reported that diazinon had not been found to be teratogenic in rabbits given 7 or 30 mg/kg body weight, although the higher dose of diazinon produced cholinergic signs. Diazinon (89.2% pure) was administered orally by gastric intubation to groups of 19 to 22 New Zealand white rabbits at daily doses of 7, 25 and 100 mg/kg body weight from day 6 to 18 of gestation. On day 30 of gestation, all dams were killed and the fetuses delivered by cesarean section. At the highest-dose level, 9/22 dams died and overt signs of toxicity included tremors, convulsions, hypoactivity and anorexia. There were no statistically significant differences among the group regarding the mean number of implantations and the proportions of live, dead or resorbed fetuses. The fetal weights were similar in treated and untreated groups, and neither embryotoxicity nor teratogenicity was observed (Harris & Holson, 1981).

7.5.2.5 *Chicken*

Several studies have investigated the teratogenic potential of diazinon in chick embryos (Khera & Bedok, 1967; Misawa et al., 1981, 1982; Henderson & Kitos, 1982; Byrne & Kitos, 1983; Wyttenbach & Hwang, 1984; Kushaba-Rugaaju & Kitos, 1985). In view of the lack of teratogenicity in mammals and the lack of adequate data on cholinesterase inhibition *in ovo*, these studies are not considered relevant in the assessment of mammalian teratogenicity.

7.6 Mutagenicity and related end-points

The summary results of mutagenicity studies conducted with diazinon are presented in Table 3.

Diazinon did not induce mutations in either *Salmonella typhimurium* or *Escherichia coli*, but produced conflicting results in mouse lymphoma L5178Y cells at the *tk* locus. Unscheduled DNA synthesis was not induced in primary cultures of rat hepatocytes. A sister chromatid exchange study with human lymphocytes cultured in whole blood gave equivocal results, while negative results were obtained in three other *in vitro* studies and, *in vivo*, in bone marrow cells of dosed mice.

Table 3. Special studies on the mutagenicity of diazinon

Test system	Test object	Results	Reference
In vitro			
Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538; *E. coli* WP2 uvrA	negative	Geleick & Arni (1990)
Ames	*Salmonella typhimurium* TA1535, TA1536, TA1537, TA1538	negative	Marshall et al. (1976)
Mouse lymphoma assay	Mouse lymphoma cells, L5178Y/tk +/-	negative	Dollenmeier & Müller (1986)
Mouse lymphoma assay	Mouse lymphoma cells L5178Y/tk +/-	positive	McGregor et al. (1988)
Sister chromatid exchange study	Chinese hamster cells V79	negative	Chen et al. (1981)
Sister chromatid exchange study	Human lymphoid cells (LAZ-007)	negative	Sobti et al. (1982)
Sister chromatid exchange study	Chinese hamster V79 cells	positive	Matsuoka et al. (1979)
Sister chromatid exchange study	Whole blood human lymphocytes	equivocal	Murti & Haworth (1990a)
Sister chromatid exchange study	Chinese hamster V79 cells	negative	Kuroda et al. (1992)
Sister chromatid exchange study	Chinese hamster V79 cells	negative	Nishio & Uyeki (1981)
Nucleus anomaly	Chinese hamster V79 cells	negative	Hool & Muller (1981c)
Chromosomal aberration	Human lymphocytes	questionable	Lopez & Carrascal (1987)

Table 3 (contd).

Test system	Test object	Results	Reference
Chromosomal aberrations	Human lymphocytes	negative	Lopez et al. (1986)
DNA repair test	Rat hepatocytes	negative	Hertner & Arni (1990)
In vivo			
Nucleus anomaly	Chinese hamster bone marrow cells	negative	Hool & Müller (1981c)
Micronucleus test	Mouse bone marrow cells	negative	Ceresa & Puri (1988)
Dominant lethal study	Mouse, male	negative	Fritz (1975)
Chromosome aberrations	Mouse spermatogonia	negative	Hool & Müller (1981d)
Chromosome aberrations	Mouse spermatocytes	negative	Hool & Müller (1981b)
Chromosomal loss	*Drosophila melanogaster*	negative	Woodruff et al. (1983)
Sister chromatid exchange study	Mouse bone marrow cells	negative	Murli & Haworth (1990b)

Chromosomal aberrations were not induced in cultured human lymphocytes. In *Drosophila melanogaster*, diazinon did not induce either complete or partial chromosome loss.

Nuclear anomaly tests in cultured Chinese hamster V79 cells and in bone marrow cells of dosed Chinese hamsters gave negative results. A micronucleus test in bone marrow polychromatic erythrocytes of mice was also negative.

No chromosomal aberrations were induced in the spermatogonia or spermatocytids of dosed mice and a dominant lethal test in dosed male mice was negative. It was concluded that diazinon is not genotoxic.

7.7 Carcinogenicity

7.7.1 Mice

Groups of 50 $B6C3F_1$ mice of each sex were treated with diazinon (98% pure) at dietary concentrations of 100 and 200 mg/kg diet for 103 weeks. Two additional groups of 25 males and 25 females each served as untreated controls. Hyperactivity was reported for the dosed mice but was rare in the control group. The body weight gains for all dosed male mice were similar to the control group except for the last 20 weeks of the study period. The treated females showed slightly lower body weights than the controls. The survival at 78 weeks in the control 100 and 200 mg/kg groups, respectively, was: males, 21/25 (84%), 45/50 (90%), 49/50 (98%); females, 24/25 (96%), 50/50 (100%), 49/50 (98%). Several neoplasms were observed, but apart from lower neoplasms in male mice none appeared to be treatment-related or had an incidence in treated groups significantly different from that of controls. The incidences of hepatocellular carcinomas in the control, 100 and 200 mg/kg groups, respectively, were: 4/21 (19%), 20/46 (43%) and 10/48 (21%). The corresponding incidences of hepatocellular carcinomas or adenomas were 5/2 (24%), 20/46 (43%) and 13/48 (27%). The Cochrane-Armitage test for trend was significant for carcinomas, but not for liver carcinomas and adenomas combined. Fisher's exact test for comparison of a dosed group with its matched control groups was significant (P=0.046) only for hepatocellular carcinomas alone in the 100 mg/kg group of male mice. In view of the lack of a dose-related response, the occurrence of

liver tumours in male mice could not be clearly attributed to diazinon (NCI, 1976).

A report submitted to the United Kingdom Ministry of Agriculture, Fisheries and Food (MAFF, 1991) described a two-year combined chronic toxicity/carcinogenicity study conducted with male and female $B6C3F_1$ mice (60/dose/sex) administered diets containing diazinon at 0, 100, 200 or 300 mg/kg (males only) or 400 mg/kg (females only). Ten mice of each sex per group were killed at 12 months. After 24 months, there were reported to be no treatment-related gross or histopathological findings. This study provides no evidence for the carcinogenicity of diazinon in mice. In particular, it does not confirm the observations described in the above-mentioned study on $B6C3F_1$ mice.

7.7.2 Rats

Groups of 50 male and 50 female Fischer-344 rats received diazinon (98% purity) at dietary concentrations of 400 and 800 mg/kg for 103 weeks. All survivors were killed at 105 weeks. An additional control group of 25 males and 25 females received an untreated diet. There was no significant effect of treatment upon body weight gain. Hyperactivity was noted in males and females of the 800 mg/kg group and males of the 400 mg/kg group. Urine was discoloured in females of the 800 mg/kg group and in dosed females there was vaginal bleeding and discharge. Survival at 78 weeks in control, 400 mg/kg and 800 mg/kg groups, respectively, were: males, 24/25 (96%), 49/50 (98%), 49/50 (98%); females, 23/25 (92%), 44/50 (88%), 44/50 (88%). Various neoplasms were observed, but only the incidence of lymphomas/leukaemias in dosed groups of males was significantly different from the controls. The incidences in the control, 400 and 800 mg/kg groups, respectively, were: males, 5/25 (20%), 25/50 (50%), 12/50 (24%); females, 2/25 (8%), 6/50 (12%), 6/50 (12%). The Fisher's exact test for comparison with the matched control was significant ($P=0.011$) only in the 400 mg/kg group of males. In view of the lack of a dose-related response, the occurrence of lymphomas/leukaemias in male rats could not be clearly attributed to diazinon. The frequency of endometrial stromal polyps was increased in the dosed groups. This lesion, which is commonly observed in Fischer-344 rats, occurred at incidences in the control, 400 mg/kg and 800 mg/kg groups, respectively, of 2/23 (9%), 8/43 (19%) and 11/49 (22%). The carcinogenic status of diazinon in this study is unclear (NCI, 1979).

The chronic toxicity study of Kirchner et al. (1991) described earlier (section 7.3.1) included groups of male and female Sprague-Dawley rats (approximately 20/dose/sex, progressing for longer than 57 weeks) administered diets containing diazinon at concentrations 0, 0.1, 1.5, 125 or 250 mg/kg. No treatment-related increases in neoplasms were observed. This study does not provide supportive evidence for a carcinogenic effect of diazinon in rats.

A report submitted to the United Kingdom Ministry of Agriculture, Fisheries and Food (MAFF, 1991) described a 120-week combined chronic toxicity/carcinogenicity study conducted with male and female F-344 rats (75/dose/sex) administered diets containing diazinon (0, 0.1, 1.5 or 22.6 mg/kg body weight per day). Rats of both sexes in the highest-dose group that died late in the study (after week 105) showed increased ulceration of the forestomach, with associated increased incidence of acanthosis, hyperkeratosis, submucosal granulation tissue and hyperplasia of the epithelium. Apparently, no neoplastic lesions were observed in the study. This study provides no evidence for the carcinogenicity of diazinon in rats. In particular, it does not confirm the observations described in the above-mentioned study on F-344 rats.

It is concluded that diazinon is not carcinogenic in rats or mice.

7.8 Special studies

7.8.1 *Neurotoxicity*

In a range-finding experiment, groups of four domestic hens (red heavy breed) were treated at four dose levels of diazinon (87% pure), and an acute oral LD_{50} of 12.5 mg/kg body weight was determined. A schedule was developed to protect the hens from acute cholinergic effects. Atropine (10.0 mg/kg intramuscular) was administered prior to the treatment with diazinon, and 2-PAM was injected at doses of 50 mg/kg at the time of the diazinon administration. In addition, the hens received post-treatment protection with concurrent doses of atropine and 2-PAM after approximately 1 and 5 h and as necessary thereafter. In the main neurotoxicity study, diazinon was given as a single dose of 28 mg/kg body weight by gastric intubation to a group of 18 atropine-pretreated hens. All hens were observed for three weeks and again treated with 13 mg diazinon/kg on day 21. The second observation period also lasted for three weeks (day 22-42). Additional

groups, which served as negative controls, were given the vehicle (10 hens treated with 1 ml/kg corn oil), and eight hens, treated with tri-*o*-tolyl phosphate (500 mg/kg) served as positive controls. One diazinon-treated hen died 5 days after the first dose and another one 6 h after the second dose. One hen from a negative control group died on day 7. There were no neurotoxic signs apparent during either of the two observation periods in the negative control group or in the treated groups. No histopathological changes in the brain, spinal cord or peripheral nerves were detected (Jenkins, 1988).

In a further test for delayed neuropathy Classen (1996) gave 20 hens a single oral dose of 100 mg diazinon/kg body weight. Therapeutic treatment with physostigmine and atropine for up to 48 h resulted in survival of 17 hens, despite a peak inhibition of brain cholinesterase by 83%. No ataxia was seen over a 28-day survival period, and no inhibition of either brain or spinal cord neuropathy target esterase (NTE) was seen at either 24 (n=5) or 48 (n=5) h.

Diazinon (88% purity) was administered by gavage to 15 rats per sex and dose at single doses of 0, 2.5, 150, 300 and 600 mg/kg. A negative control group of 15 animals per sex received the vehicle (corn oil) only. A group of 10 animals per sex served as positive control and was administered a single dose of 150 mg/kg triademefon 60 min prior to the Functional Observational Battery (FOB). Two males and one female dosed at 600 mg/kg died. A transient reduction in body weight and body weight gain was observed in males dosed at 300 and 600 mg/kg during week one. Food consumption was reduced in the same males, and in females dosed at >150 mg/kg. These findings decreased in incidence and severity with decreasing dose. No treatment-related effects were observed in the FOB on study days 8 and 15. In males dosed above 150 mg/kg and in females dosed above 2.5 mg/kg, activity counts in the figure-8 maze were significantly decreased at the estimated time of peak effect only. Serum cholinesterase activity was significantly decreased at the time of peak effect in all diazinon-treated groups. Full recovery was observed in all groups on study day 15. Red blood cell cholinesterase activity was significantly inhibited on study day 1 in animals of both sexes treated with >150 mg/kg. Substantial recovery was observed on study day 15, but significant inhibition still remained. No inhibition of brain cholinesterase activity was detected on day 15. No neuropathological effects were noted for diazinon at necropsy or upon histopathological examination. It was concluded that the administration of diazinon resulted in reversible neurotoxicity and

cholinergic poisoning without neuropathological changes. The NOAEL was 2.5 mg/kg body weight for both sexes (Chow & Richter, 1994).

7.8.2 Effects on enzymes and transmitters

Male rats were treated bi-weekly by gavage with the equivalent of 0.5 mg/kg per day technical diazinon for up to 28 weeks. The animals were killed at specific time intervals (7, 14 and 28 weeks) and compared with age-matched controls. Blood and brain tissues were analysed for cholinesterase activity and for concentrations of catecholamines and amino acids. Only plasma cholinesterase activity was significantly reduced. Erythrocyte cholinesterase and brain cholinesterase were unchanged while during the same period the levels of several putative brain neurotransmitters, aspartate, glutamate (excitatory) and taurine as well as GABA (inhibitory) were significantly reduced in experimental versus control animals. Blood serotonin level was significantly elevated but no other blood or brain monoamines were significantly altered. Whilst the authors (Rajendra et al.,1986) concluded that oral administration of diazinon exerts effects on brain neurotransmitters, even at the low-dose levels administered in this study, the biological significance of these findings is unclear.

Intraperitoneal administration of diazinon diminishes formation of L-kynurenine by liver slices from 93% at 1 mg/kg dose to 56% at 40 mg/kg. The ratio of critical intermediates in L-tryptophan biosynthetic pathway, L-kynurenine to *N*-formyl-L-kynurenine, decreases and is reversed with increasing dosage of diazinon (Seifert & Cassida, 1979).

Diazinon altered the formation of several L-tryptophan metabolites associated with the L-kynurenine pathway in mice. Liver kynurenine formamidase was inhibited almost completely by diazinon (10 mg/kg). The enzyme inhibition resulted in reduced L-kynurenine biosynthesis in livers and a concomitant accumulation of *N*-formyl-L-kynurenine. However, in plasma, L-kynurenine level increased up to 5-fold in diazinon-treated mice. Consequently, the urinary excretion of xanthurenic acid and kynurenic acid was raised 5- to 15-fold. The revelation of this novel mechanism of diazinon action is an important piece of information needed for a better understanding of the non-

cholinergic toxicity of organophosphorus acid triesters and methylcarbamates (Seifert & Pewnim, 1992).

7.8.3 *Effects on the immune system*

Pregnant F_2 dihybrid female mice received either a vehicle or 1 of 2 doses of diazinon (0.18 (n=19) or 9.0 (n=21) mg/kg body weight) in the diet, daily throughout gestation. All mothers gave birth to viable, overtly normal offspring at term. However, a significant number (12%) of pups born to dams who received 9.0 mg/kg died prior to weaning on day 28; necropsy findings were consistent with death from respiratory infection. There was no significant difference in mortality between control and diazinon-treated offspring once they reached 28 days of age. Determinations of five different classes of serum immunoglobulin (Ig) concentrations (IgG1, IgG2a, IgG2b, IgA, IgM) at 101, 400 and 800 days of age indicated transient but consistent disturbances of 2 Ig classes in offspring as a result of prenatal diazinon exposure. IgG1 concentrations of male offspring exposed to 0.18 mg/kg were significantly elevated at 101 days but not at 400 or 800 days of age. IgG1 concentrations of female offspring exposed to 9.00 mg/kg were significantly depressed at 101 days but not different from controls at 400 or 800 days of age. Changes in IgG2b levels generally were similar to those recorded for IgG1 but of smaller magnitude. There were no significant effects on serum IgG2b or IgM concentrations, and only equivocal effects on IgA, as a consequence of prenatal exposure to either pesticide. This study offers no conclusive information of an effect of diazinon on the immune system (Barnett et al., 1980).

7.8.4 *Effect on pancreas*

Diazinon has been reported to cause acute pancreatitis and ductal hypertension in dogs, which is due to the absence of acetylcholinesterase in pancreatic sphincter, duodenal smooth muscle in dogs and a reliance upon the more readily inhibited butyrylcholinesterase (Dressel et al., 1980; Frick, 1987).

Kazacos (1991) examined the toxic effects of diazinon on the guinea-pig pancreas. Guinea-pigs were given single intravenous dose of diazinon at concentration ranging from 125 to 200 mg/kg body weight. Examination of pancreatic tissue from animals killed at various time intervals after dosing revealed acinar cell vacuolization

after 24 h. This cellular injury disappeared within 3 days after the initial toxic insult. These are considered to be species-specific effects.

7.9 Factors that modify toxicity; toxicity of metabolites

7.9.1 Metabolic enzymes

Abdelsalam & Ford (1986) found that the toxic effects of diazinon were increased by pretreatment with the hepatic microsomal enzyme inducers dieldrin and phenobarbitone and that, at the same time, there was a rise in the liver carboxylesterase activity. In this experiment, the toxicity of diazinon increased when calves were pretreated with dieldrin or phenobarbitone despite the increased activity of the liver carboxylesterase. Apparently carboxylesterase activity was not sufficient to protect against the toxicity of diazinon in the pretreated calves. This suggests that either the increased carboxylesterase activity had only a minor role in the hydrolytic detoxification of diazinon or active metabolites, or that its effect might have been overwhelmed by the action of other microsomal oxidase activity concurrently induced by dieldrin and phenobarbitone leading to a faster rate of activation than degradation of diazinon.

Abdelsalam & Ford (1987) described the effect of induced liver and kidney lesions on the toxicity of levamisole and diazinon, two antihelmintics routinely used in ruminant livestock management, and of a lung lesion on the toxicity of diazinon in calves. Hepatic or renal damage such as may occur naturally as a consequence of infection or of the ingestion of poisonous plants or other toxic substances is, therefore, likely to affect the metabolism and excretion of drugs routinely used in antihelmintic control programmes. Liver damage in calves, induced by the oral administration of the flukecide, carbon tetrachloride, increased the toxic effect of diazinon but not of levamisole, whereas the presence of a renal tubular lesion caused by mercuric chloride enhanced the toxicity of both commonly used antihelmintic compounds.

7.9.2 Antidotes

The effects of atropine/oxime therapy on diazinon-poisoned animals was investigated in rats and rabbits. The rats were orally treated with 235 mg/kg body weight (0.8 LD_{50}) of diazinon (91.9% pure), while rabbits received 1600 mg diazinon/kg body weight by the

subcutaneous route. In both species, intramuscular administration of 16 mg/kg atropine (10 min post treatment), and 30 mg/kg of pyridine 2-aldoxime methochloride (2-PAM Cl) 24 h later, significantly increased the reactivation of the diaphragm cholinesterase. The oral LD_{50} for diazinon in the rat was increased by a factor of 1.7 when 2-PAM Cl was administered intravenously and 3.1 times when 2-PAM Cl was given orally. In order to prevent the reappearance of signs the authors recommended that 2-PAM Cl be administered intravenously at the same time as atropine followed by repeat oral administrations, as needed (Harris et al., 1969).

The antidotal efficacy of pralidoxime iodide and obidoxime dichloride was investigated in goslings poisoned by a supralethal dose of diazinon. Various doses of both drugs were administered by intramuscular injection when the poisoned birds were unable to walk. Pralidoxime at 100 mg/kg induced recovery in 4 out of 6 poisoned goslings, and 25 mg/kg successfully treated only 1 of 6 birds. Obidoxime at 25 mg/kg showed no therapeutic properties, whereas 50 and 100 mg/kg delayed the death of some birds by several hours. At 100 mg/kg, all goslings had transient signs of intoxication, which precluded the use of this compound as an antidote at higher doses (Shlosberg et al., 1976).

7.9.3 Potentiation

In a study of the potentiation of the acute toxicity of diazinon by several other pesticides (chlordimeform, iodofenphos, profenphos, methacrifos), there was no potentiation at equitoxic doses (Sachsse & Bathe, 1975, 1976, 1977, 1978).

8. EFFECTS ON HUMANS

8.1 Exposure of the general population

8.1.1 Acute toxicity, poisoning incidents

Several cases of intentional (Kabrawala et al., 1965; Banerjee, 1967; Wadia et al., 1974; Klemmer et al., 1978; Poklis, 1980; Wedin et al., 1984; Hodgson & Smith, 1992) and accidental acute poisoning with diazinon have been reported. Accidental poisonings were usually due to ingestion of improperly stored liquid formulation (Hayes, 1963; Zwiener & Ginsburg, 1988; Weizman & Sofer, 1992; Hodgson & Smith, 1992). Cases of poisoning after cutaneous application of diazinon for lice treatment have also been described (Muratore et al., 1960; Hayes, 1963; Halle & Sloas, 1987). Several accidents involved children (Mizra et al., 1972; English et al., 1970; Zwiener & Ginsburg, 1988; Hodgson & Smith 1992; Weizman & Sofer, 1992; Wagner & Orwick, 1994).

Generally, symptoms and signs were typical of AChE inhibition, which responded to atropine and oxime treatment. In a case of fatal suicidal ingestion of diazinon reported by Poklis et al. (1980), diazinon concentrations in postmortem body fluids and tissues were found to be 277 mg/litre in blood, 200 mg/litre in the bile and 15 mg/kg in adipose tissue. In the stomach 44 mg were found. Cases with atypical or unusual features are described in section 8.1.1.3. No cases of delayed polyneuropathy have been observed, as would be expected from the negative animal data. The following sections deal with some specific aspects of acute poisoning by diazinon (i.e., the acute pancreatitis, the intermediate syndrome, and some unusual case reports).

8.1.1.1 Acute pancreatitis

Increased levels of serum amylase and glucose have been described in some severe cases of diazinon poisoning. In certain cases these enzymatic alterations were accompanied by prominent abdominal symptoms and signs, including abdominal rigidity. All these were considered indicative of acute pancreatitis (Dressel et al., 1979; Dagli et al., 1981; Lee, 1989; Weizman & Sofer, 1992). On one occasion a pancreatic cyst was observed (Dressel et al., 1979). In all cases, pancreatitis was mild and patients fully recovered. Severe

poisoning with other organophosphates, e.g., parathion (Weizman & Sofer, 1992), coumaphos (Lee, 1989) and malathion (Lee, 1989), was also associated with acute pancreatitis. Apparently, poisoning with an unknown carbamate was also associated with acute pancreatitis (Weizman & Sofer, 1992).

8.1.1.2 *Intermediate syndrome*

Senanayake & Karalliedde (1987) described a syndrome caused by organophosphate pesticides and named it "intermediate", because its onset was delayed after cholinergic syndrome but appeared earlier than polyneuropathy. The syndrome, appeared 24-96 h after poisoning during recovery from the cholinergic crisis. It was characterized by paralysis of proximal limb muscles, neck flexors, motor cranial nerves and respiratory muscles. It was resistant to atropine treatment and, in certain patients, required assisted ventilation. It is noteworthy that Wadia et al. (1974), reporting the neurological manifestations seen in 200 consecutive cases of poisoning, mostly with diazinon, described two different types of signs: type I, characteristic of the cholinergic syndrome and responsive to atropine, and type II, present in about 20% of the cases, which appeared at least 24 h later, resembled those of the intermediate syndrome and were not responsive to atropine (Wadia et al., 1974).

Other cases of intermediate syndrome due to diazinon poisoning have been described (Hall & Baker, 1989; Samal & Sahu, 1990).

8.1.1.3 *Unusual case reports*

Three-week-old twins were hospitalized because of respiratory distress. One was cyanotic on admission, but both had rapid shallow breathing, profuse nasal and bronchial secretions, and pinpoint pupils; muscle fasciculations were not detectable. At 48 h only the sicker twin had slightly reduced pseudocholinesterase activity. Treatment was appropriate and recovery uneventful. Investigation revealed that the babies lived in one side of a two-story house that had been divided into two apartments by partitions. About 10:30 h on the previous day the other apartment had been sprayed with 1% diazinon for cockroach control using approved spot applications directed mainly at cracks. The twins were the only ones who had remained indoors. The observed degree of respiratory distress in the presence of little or no

inhibition of cholinesterase was consistent with exclusively respiratory exposure (English et al.1970).

A 12-week-old infant girl developed persistent hypertonicity of the extremities without other signs of intoxication. It was discovered that the organophosphate insecticide diazinon was applied in her home 5 weeks prior to the onset of signs. Six months after application, high levels of diazinon residues were found on the floor (230 ng/cm^2), in vacuum cleaner dust (1700 mg/kg), and in the air (2.8 ng/m^3). A diazinon dose of approximately 0.02 mg/kg per day was calculated and derived from the infant's urine level of diazinon metabolites determined 6 months after application of diazinon in her home. Her muscle tone returned to normal shortly after the infant was removed from the home (Wagner & Orwick, 1994).

According to Hata et al. (1986), atypical ocular bobbing resulted from an intentional poisoning from diazinon. The authors suggest acetylcholine as a neurotransmitter substance within the ocular motor pathway.

A 26-year-old man, who ingested approximately 230 ml of a solution of an unknown concentration of diazinon in a suicide attempt, developed a severe cholinergic syndrome which was relived by atropine and 2-PAM. Diuresis was greatly reduced (22 ml/h) and urine was dark and cloudy (specific gravity 1.029). It is possible that significant dehydration may have precipitated this reaction (Wedin et al., 1984; Albright, 1984).

8.1.2 Controlled human studies

A cumulative toxicity study was conducted with human volunteers. Four healthy males weighing between 74 and 96 kg and aged between 30 and 45 years ingested diazinon in gelatin capsules (95.4% pure) at a dose of 0.025 mg/kg per day. Two males received 34 consecutive treatments (Group B), while the two other volunteers were treated for 4 days, were left untreated for the next 5 days in order to investigate reversibility of the effects and then received the capsules again for 32 more days (Group A). The daily dose was split into three administrations taken after meals around 9, 13 and 19 h. Parameters of haematology, urine analysis and blood biochemistry (plasma and erythrocyte cholinesterase, serum alkaline and acidic phosphatase activities) were determined at regular intervals. A reversible decrease

of plasma cholinesterase activity was observed in group A during the first 4 days of treatment while the erythrocyte cholinesterase activity remained unaffected. During the second treatment period of group A and during the entire treatment of group B, the cholinesterase activities were similar to those observed at pretest. No clinical signs or changes in other parameters were noted. It was concluded that the administered daily dose of 0.025 mg/kg marginally inhibited the plasma cholinesterase only, and can therefore be considered as a NOAEL in humans (Payot, 1966).

8.2 Occupational exposure

8.2.1 Acute poisoning

Poisoning following occupational exposure to diazinon was usually associated with improper or prolonged storage of the commercial formulations, which, prior to the improvements carried out by the manufacturer, tended to give rise to more toxic impurities (mainly TEPP).

Soliman et al. (1982) investigated two spraymen who had a cholinergic syndrome (with about 90% red blood cell AChE inhibition) after using a commercial formulation of diazinon which was packaged in tin-plated cans that had replaced the more expensive aluminium cans. Analysis of such commercial formulation revealed the presence of TEPP, sulfo-TEPP, monothiono-TEPP and other impurities, but no diazinon.

Mello et al. (1972) reported an episode where three farmers were poisoned when using a commercial formulation of diazinon that was transferred from the original container to another container and then stored for some time. This formulation contained monothiono-TEPP and was about 30 times more toxic to rats than a recently prepared and properly stored formulation. On that occasion, 26 of 40 cows died when treated against tick infestation with this formulation.

A fatal case of poisoning by diazinon and malathion, possibly by inhalation, was described by Wecker et al. (1985). The 51-year-old man was found unconscious in the closed shed where he sprayed three cows with the pesticides.

Two cases of cutaneous hepatic porphyria of toxic origin were identified within a short period of time. Both patients were farmers and recently handled very intensively, without any precaution, some pesticides containing organophosphorus substances (diazinon). The symptoms were similar to those of the so-called Turkish porphyria (Bopp & Kosminsky, 1975).

8.2.2 Effect of short-term and long-term exposure

Neurophysiological investigations and determinations of blood cholinesterase activities were carried out on 11 Swedish spraymen exposed to bromophos, diazinon, dursbane and malathion. Plasma cholinesterase activity was significantly reduced after work, while erythrocyte cholinesterase activity was unchanged. In none of the workers with a decreased plasma cholinesterase activity after work could any related acute neuromuscular disturbance be detected when the men were tested with repetitive nerve stimulation and with single fibre electromyography. Signs of subclinical neuropathy were present as a slight reduction in sensory conduction velocity and increased fibre density in some workers (Stalberg et al., 1978).

A cohort of 99 workers exposed to diazinon was tested before and after the work shift with a neurobehavioural test battery, which included a brief examination, a symptom questionnaire and tests of concentration, eye-hand coordination, pattern recognition, visual memory and finger tapping. The median diazinon exposure level was 2.1 mg/day and the mean duration of exposure was 39 days (see section 5.3). There was no correlation between the diethylthiophosphate (DETP) concentrations or diazinon exposure and pre- or post-shift neurobehavioural function with linear regression models after adjusting for age, sex, education and alcohol intake. The study failed to demonstrate adverse behavioural effects of repeated, low-level diazinon exposure (Maizlish et al., 1987).

Three groups of agricultural workers with a history of exposure to organophosphate pesticides were followed up to evaluate the utility of sequential post-exposure cholinesterase analyses to confirm organophosphate intoxication in the absence of baseline cholinesterase values. Three or more cholinergic symptoms were reported by 50 of the 72 patients. Pre-exposure red blood cell cholinesterase activities of 45 workers were above the lower limit of laboratory normal range. Follow-up examinations, including blood cholinesterase activity

analyses, were conducted in 57 subjects. When final post-exposure cholinesterase activity determinations were compared with respective individual normal baseline values, the plasma and red blood cell activities were shown to be inhibited. The data support the use of sequential post-exposure blood cholinesterase analyses to confirm the diagnosis of organophosphate-induced illness in the absence of baseline values (Coye et al., 1987).

Of 67 described poisoning incidents in California involving 583 people, nineteen involved a pesticide product containing an organophosphate: most often chlorpyriphos (8), diazinon (3) and malathion (5). There were also 10 cases that resulted from suicide, and two cases involved diazinon (Maddy & Edmiston, 1988).

In a study of organophosphate-induced contact dermatitis in 202 patients in Japan, Matsushita et al. (1985) attributed the reactions mainly to diaoxabenzafos, fenitrothion, leptophos, cyanophos, diazinon and malathion. The areas affected by dermatitis were fingers (62.4%), face (39.6%), forearm (31.6%) and neck (29.7%). One quarter of the cases with dermatitis had symptoms associated with acute organophosphate poisoning.

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

9.1 Microorganisms

Singh (1973) found that three genera of cyanobacteria (blue-green algae) tolerated diazinon at concentrations of 300 and 400 mg/litre. Clegg & Koevening (1974) indicated that the population densities of three species of freshwater algae were relatively unaltered by a concentration of 100 mg/litre. Butler et al. (1975) demonstrated that diazinon inhibited growth of numerous species of green algae and cyanobacteria at concentrations of 0.01 mg/litre and 0.1 mg/litre. Wong & Chang (1988) studied the effects of diazinon on the growth of the green alga, *Chlamydomonas reinhardtii*. They observed a reduction in growth at concentrations of 5 and 10 mg/litre and complete inhibition at 20 and 40 mg/litre.

Doggett & Rhodes (1991) determined the effects of diazinon on phytoplankton population dynamics. The objectives of this study were to determine the effects of diazinon (1, 5, 10, 20 and 40 mg/litre concentration) on the growth rates of three widely distributed species of freshwater algae, and to ascertain the effects of this pesticide on the diversity of a natural phytoplankton assemblage. Stimulation of growth was exhibited by *Selenastrum capricornutum* and *Chorella* exposed to diazinon at 1 and 5 mg/litre. The higher concentrations of 10, 20 and 40 mg/litre all inhibited growth. The growth rates of the cyanobacteria showed a high degree of tolerance; a suppression of growth was observed only at 40 mg/litre. Two genera of green algae were stimulated by all concentrations.

The acute toxicity of diazinon to the freshwater rotifer *Brachionus calyciflorus* was determined after 24 h of exposure; the mean LC_{50} value was 29.2 mg/litre. Based on this result, four sublethal concentrations were chosen to determine the median lethal time (LT_{50}) at each concentration of diazinon tested. The concentrations tested were 1/5, 1/4, ½ and 2/3 of the LC_{50} (24 h). The LT_{50} values ranged from 6.96 to 2.49 days after diazinon exposure, decreasing with increasing exposure concentration (Fernandez-Casalderrey et al., 1992).

Several species of soil-borne fungi invade plant roots forming vascular-arbuscular mycorrhizae which aid in growth and nutrient element absorption. Pre-plant incorporated treatments at 2 and 4 kg/ha of trifluralin and diazinon had no significant effect on growth, phosphorus accumulation or root colonization by mycorrhizal fungi in soybeans planted in an Andover clay loam. At currently used commercial rates, diazinon did not affect mycorrhizal development under the conditions of the experiment (Burpee & Cole, 1978).

Nitrogenase activity of excised soybean nodules was severely affected by diazinon following application of 3, 1, 0.5 and 0.25 multiples of the amounts stated on the label (Hensley, 1991).

9.2 Aquatic invertebrates

Acute toxicity of diazinon to aquatic invertebrates is summarized in Table 4.

The effect of diazinon (Basudine, 0.01, 0.1, 1.0 mg/litre) on the physical and chemical properties of haemolymph of *Lymnaea stagnalis* (L.) and *Planorbius corneus* (L.) infected with trematodes was studied by Stadnichenko et al. (1987). Haemolymph viscosity and density decreased after the treatment.

Robertson & Mazzella (1989) determined the toxicity of diazinon to the freshwater snail *Gillia altilis*. Based on nominal calculations, the LC_{50} values for static 4- and 96-h exposures were 340 mM (93 mg/litre) and 40 mM (11 mg/litre), respectively.

Experiments were conducted to determine the effects of piperonyl butoxide, a synthetic methylenedioxyphenyl inhibitor of cytochrome(s) P-450, on the toxicity of organophosphate insecticides to three cladoceran test species: *Ceriodaphnia dubia*, *Daphnia magna*, and *Daphnia pulex*. The acute toxicity of diazinon to three tests species was similar, with LC_{50} values ranging from 0.50 to 0.80 mg/litre. Co-administration of piperonyl butoxide effectively reduced the acute toxicity of metabolically activated diazinon, and piperonyl butoxide concentrations of 500 or 1000 mg/litre completely blocked the toxicity of diazinon at concentrations of up to 16 times the 48-h LC_{50}. In the case of *D. pulex*, piperonyl butoxide at 500 mg/litre also significantly reduced the toxicity of diazinon at concentrations of up to 16 times the 48-h LC_{50} (Ankley et al., 1991).

Table 4. Acute toxicity (LC_{50}) to aquatic invertebrates

Species	Duration (h)	Concentration (mg/litre)	Reference
Snail (*Gillia altilis*)	96	11	Robertson & Mazzella (1989)
Cladocerans	48	0.0005-0.0008	Ankley et al. (1991)
Cladoceran (*Daphnia pulex*)	48	0.001 (0.0006-0.0011)	Mayer & Ellersieck (1986)
Cladoceran(*Simocephalus serrulatus*)	48	0.0014 (0.0012-0.0016) at 21 °C	Mayer & Ellersieck (1986)
		0.0018 (0.0014-0.0022) at 15 °C	
Scud (*Gammarus fasciatus*)	96	0.0002 (0.00015-0.00028)	Mayer & Ellersieck (1986)
Shrimp (*Hyallela azteca*)	96	0.004-0.006	Collyard et al. (1994)
Desmocaris trispimosa	96	0.0208 (0.0192-0.0224)	Ebere & Akintonwa (1992)
Shrimp (*Palaemonetes africanus*)	96	0.0179 (0.0147-0.020)	Ebere & Akintonwa (1992)
Insect larva (*Pteronarcys californica*)	96	0.025 (0.020-0.030)	Mayer & Ellersieck (1986)

9.3 Fish

The acute toxicity of diazinon to fish is summarized in Table 5.

The median lethal concentration (LC_{50}) of diazinon was determined for *Clarias batrachus*; the LC_{50} for 40 days of exposure to diazinon was 2.4 mg/litre (Tripathi, 1992). The acute toxicities (24, 48, 72 and 96 h) of eight pesticides to *Anguilla anguilla* were determined. The 24- to 96-h LC_{50} values for diazinon ranged from 0.16 to 0.8 mg/litre (Ferrando et al., 1991).

Bresch (1991) studied the effects of diazinon on early life-stages in zebrafish. Zebrafish kept at diazinon concentrations of 0.2, 0.04 and 0.008 mg/litre grew alike, and no differences among the groups were observed. Survival rates of animals of different groups did not differ either. In no groups were abnormal fish seen.

Whereas growth and survival of fathead minnows were not influenced at concentrations below 0.2 mg/litre in a test described by Allison & Hermanutz (1977), the minnows responded more sensitively in a similar test by another laboratory: effects were observed below 0.08 mg/litre (Jarvinen & Tanner, 1982). Allison (1977) found reduced larval growth of the flagfish if reared in water containing diazinon at a concentration of 0.014 mg/litre.

Brain acetylcholinesterase (AchE) activity and changes in optomotor behaviour were determined in bluegill sunfish, *Lepomis macrochirus*, exposed to graded concentrations (0, 15, 30, 5, 60 and 75 µg/litre) of diazinon for a period of 24 h (Dutta et al., 1992). A significant decrease of AchE activity was observed at and above an exposure concentration of 45 µg/litre, whereas a decline in the scores of the "following" responses of the fish was observed at an exposure concentration of 30 µg/litre.

Weiss (1961) was the first to investigate *in vivo* brain AChE activity of fish exposed to organophosphates. He found that the extent of enzyme inhibition was proportional to the concentration of the substance and extent of exposure, and suggested that fish brain AChE activity could be used to detect the presence of anticholinesterases in the aquatic environment.

Table 5. Acute toxicity (LC_{50}) to fish

Species	Duration (h)	Concentration (mg/litre)	Reference
Bluegill sunfish (*Lepomis macrocharis*)	96	0.17 (0.012-0.22)	Mayer & Ellersieck (1986)
Rainbow trout (*Oncorynchus mykiss*)	96	0.09	Mayer & Ellersieck (1986)
Cutthroat trout (*Salmo clarkii*)	96	2.76 (2.28-3.33) in soft water 1.7 (1.39-2.09) in hard water	Mayer & Ellersieck (1986)
Walking catfish (*Clarias batrachus*)		2.41	Tripathi (1992)
Eel (*Anguilla anguilla*)	96	0.08 (0.06-0.10)	Ferrando et al. (1991)
Channel catfish (*Channa punctatus*)	96	3.1	Sastry & Malik (1982a)
Goby (*Gobius*) sp.	96	0.25 (0.23-0.28)	Ebere & Akintonwa (1992)
Lake trout (*Salvelinus namaycush*)	96	0.6 (0.4-0.9)	Mayer & Ellersieck (1986)

Table 6. Summary of brain acetylcholinesterase activity inhibition by diazinon in aquatic organisms

Organism	Exposure concentration (mg/litre)	Duration (h)	Inhibition (%)	Reference
Bluegill	0.1	6	95	Weiss (1961)
Fathead minnow	0.1	18	70	Weiss (1961)
Goldfish	0.1	18	43	Weiss (1961)
Golden shiner	0.1	18	40	Weiss (1961)
Sheepshead minnow	6.5	24	71	Goodman et al. (1979)

Goodman et al. (1979) reported a dose-dependent inhibition of brain AChE activity in sheepshead minnows for diazinon. For the same sublethal exposure (6.5 mg/litre), inhibition was independent of the exposure duration, being 68 and 78% on days 4 and 108, respectively. The authors found that the brain AChE activity of sheepshead minnows exposed to diazinon varied and was susceptible to exposure concentration. AChE was depressed long after no measurable diazinon was found in exposed sheepshead minnows.

The effect of acute exposure to diazinon (3.1 mg/litre for 96 h) and chronic exposure to a sublethal concentration (0.31 mg/litre) of diazinon has been studied in the liver, stomach, intestine and pyloric caeca of a freshwater teleost fish, *Channa punctatus*. In acute exposure, succinate dehydrogenase activity was elevated in intestine and pyloric caeca. No alteration was noted in lactate dehydrogenase activity but pyruvate dehydrogenase activity was inhibited in pyloric caeca. Chronic exposure resulted in inhibition of the activities of the three dehydrogenases in all four organs at both intervals (Sastry & Malik, 1982a).

Exposure to diazinon at different concentrations induced pathological changes in muscle cell organelles of *Tilapia nilotica*. The earliest changes in muscles of fish exposed to 10 mg/litre consisted of swelling of sarcoplasmatic reticulum in many fibres and the appearance of many cytoplasmatic vacuoles of different sizes. In muscle of

fishes exposed to the LC_{50} (20 mg/kg) of diazinon, fragmentation of the myofibrils occurred over the entire length of the sarcomere with involvement of both the thick myosin filament of the A-band and the thinner actin filaments of the I-band. It was speculated that these effects may be attributed to the anti-cholinesterase activity of these insecticides. (Sakr & Gabr, 1992).

Acute effect of diazinon on the intramembranous particles (IMPs) of microvilli of the intestinal epithelial cells of *Tilapia nilotica* fish was studied using the freeze-fracture technique. Exposing fish to different repeated concentrations of diazinon (½ LC_{50}) cause a significant decrease in the population density of IMPs in P and E faces. IMPs of microvilli found in intestinal epithelial cells are thought to represent many kinds of protein including enzymes. It was suggested that diazinon induced a reduction in enzymatic content of the membrane, which was accompanied by a decrease in the IMP density of the microvilli (Sakr et al., 1991). El-Elaimy et al. (1990) reported that exposure of *Tilapia nilotica* to increasing concentrations of diazinon induced ultrastructural alterations in the intestine.

Four-month old adult siblings of zebrafish (*Brachydanio rerio*) were exposed to four concentrations of diazinon for up to 168 h. DNA, RNA, protein and total free amino acid content were measured in the liver. The DNA, RNA and protein contents were significantly reduced, whereas the amino acid content was significantly enhanced. All these changes showed a dose-dependent as well as a time-dependent response (Ansari & Kumar, 1988).

Anees (1978) presented the results of sub-lethal exposure to diazinon of an adult freshwater teleost. The concentrations of insecticide used in the study were given as 0.37 mg/litre per 24 h and 0.28 mg/litre per 96 h. This was a study on the evaluation of histopathology as a possible indicator of aquatic pollution by insecticides. Hepatocytes were considerably vacuolated and reduced in size after 24 h of exposure. However, 96 h of exposure produced less vacuolization but the liver showed a foamy appearance. Damage to the hepatic blood supply and the appearance of dark, granular cytoplasmic inclusions resulted from a 14-day exposure. The same concentrations of pesticide have already been observed to cause many tissue changes in the intestine of *Channa punctatus* and disturbances in the distribution of serum proteins.

The effect of exposure to the LC_{50} (12 mg/litre) for 96 h and to a sublethal concentration (3.3 mg/litre) for 15 and 30 days was studied in the digestive system of the catfish *Heteropneustes fossilis*. The most conspicuous pathological changes in the liver were vacuolization of the cytoplasm of hepatocytes, enlargement of nuclei, rupture of cell membrane, liver cord disarray, and damage of connective tissue. Intercellular spaces were widened. In stomach the mucosa was eroded. In intestine the nuclei of the columnar epithelial cells were reduced in volume and the cytoplasm was highly degenerated. In both acute and chronic exposure alkaline phosphatase and glucose-6-phosphatase activities were inhibited significantly in the different portions of the digestive system. Acid phosphatase activity was elevated in all the portions and in both stages of exposure. In acute exposure insignificant elevation was observed in the activities of amylase and maltase, while lactase activity was inhibited. An inhibition in maltase activity was significant only in the liver. Lipase activity showed a decrease in all stages of exposures, while there was no marked alteration in activities of pepsin and trypsin (Sastry & Malik, 1982b).

9.4 Effects in mesocosms and the field

A mesocosm study was performed with 17 treated and 4 untreated ponds (each 0.1 acre in surface area and 2.2 metres deep). The ponds received multiple applications of diazinon with single applications ranging from 2 to 25 µg/litre and corresponding to total application rates of 5.7, 11.4, 22.9, 45.8 and 91.5 µg/litre. The following effects on sediment-dwelling organisms were observed: Trichoptera was the most sensitive order, with significant reductions at all treatment levels throughout most of the treatment period. Trichoptera was a minor component of the macroinvertebrate communities in the mesocosms. Diptera and Ephermeroptera were intermediate in sensitivity; both were reduced at 22.9 and 91.5 µg/litre by the end of the treatment period, though both recovered to control levels shortly after treatment ended. Odonata was the least sensitive order with effects only at 91.5 µg/litre. Total insect abundance generally followed the trend of the Diptera, which was the most abundant order; increasingly severe effects at 22.9 to 91.5 µg/litre during the treatment period was followed by recovery. The abundance of crustaceans in macro-invertebrate samples generally followed a similar pattern. Gastropods were essentially unaffected by diazinon. Though dipterans as a whole were affected only at 22.9 µg/litre or more and recovered rapidly,

some dipteran sub-taxa were more sensitive or were significantly reduced in the post-treatment period. Tanypodinae and its dominant tribe, Pentaneurini, were the most sensitive. These were significantly reduced in all treated ponds at the end of the treatment period. Both groups recovered within eight weeks of the last treatment. The sub-family Chironominae was the next most sensitive among the family Chironomidae, especially the tribes Tanytarsini and Chironomini. Tanytarsinids were reduced at 22.9 µg/litre early in the treatment period and then recovered. Chironomini followed a similar pattern, including recovery, but were again reduced in number at 22.9 to 91.5 µg/litre. The sub-family Orthocladiinae was the least sensitive chironomid group with effects only at 91.5 µg/litre and full recovery within two weeks. With the wide range of sensitivity observed among the chironomids, the overall impact of diazinon was relatively minor; statistically significant reductions were observed twice early in the highest treatment. Two less abundant dipteran families, Chaoboridae and Ceratopogonidae, were affected at 11.4 µg/litre or more. The greatest effect on Chaoboridae occurred two months into treatment and that on Ceratopogonidae occurred during the treatment period, but sporadic effects persisted beyond (Giddings, 1992).

The application of diazinon to a small stream at 3 mg/litre resulted in increased drift of benthic organisms and changes in the composition of benthic fauna. These changes were not persistent, however, as the communities were restored to normal within 4 weeks of treatment (Miller et al., 1966).

9.5 Terrestrial invertebrates

Stevenson (1978) reported LD_{50} values for bees of 0.22 µg/bee (topical) and 0.20 µg/bee (oral).

When earthworms (*Eisenia foetida*) were exposed to technical diazinon in soil, the 14-day LC_{50} was calculated to be 130 mg/kg soil. A no-observed-effect concentration of 12.3 mg/kg was reported (Vial, 1990).

In a field experiment in Connecticut, USA, diazinon was applied to tobacco fields as a 10% granular formulation at up to 4.48 kg a.i./ha; granules were raked into the soil. Mortality of earthworms

(*Lumbricus terrestris*) did not differ between treated and control plots (Kring, 1969).

9.6 Birds

Acute toxicity to birds is summarized in Table 7.

The use of diazinon for controlling flies in sheds used to house ducks led to the death of an estimated 15 600 young birds (Dougherty, 1957).

Ingestion of a few granules could be lethal to sparrow-sized birds for diazinon 14G (Hill & Camardese, 1984).

Variability of toxicity among anticholinesterase formulations was shown with a single dose of diazinon administered orally as technical grade (TG, 99% a.i.) alone or in corn oil, as granular (GR, 14-15% a.i.), or as emulsifiable concentrate (EC, 48% a.i.). The rank of the formulations tested, from most to least toxic, based on statistically separable ($p<0.05$) LD_{50}s, was EC > GR=TG > control. The difference between the least and most toxic form was nearly three-fold (Hill, 1988).

The single acute oral and dermal doses of diazinon were determined for 8- and 18-week-old broadbreasted white turkeys. The hazard to turkeys of exposure to soils treated for control of chiggers was evaluated. Diazinon was lethal for 18-week-old turkeys at 2 mg/kg orally and toxic at 5 mg/kg dermally. In spite of this high toxicity, exposing the turkeys to soil treated with 18 kg diazinon per hectare led to no poisoned birds (Radeleff & Kunz, 1972).

The activity of acetylcholinesterase (AChE) and the density of muscarinic receptors were measured in brains from normal Japanese quail (*Coturnix coturnix japonica*) and from quail after lethal intoxication with diazinon. The maximum relative loss of activity due to postmortem decomposition alone during 8 days was 13 and 10% for AChE and muscarinic receptors, respectively. During postmortem

Table 7. Acute toxicity to birds

Species	Age/weight	LD_{50}	LC_{50}	Reference
Japanese quail (*Coturnix coturnix japonica*)	50-60 days (105-195 g)	4		Sachsse (1973a)
	5 days (10-30 g)	1.1		Sachsse & Ullmann (1975a)
	50-60 days		900*	Sachsse (1972)
Bobwhite quail (*Colinus virginianus*)	14 days	5.2		Fink (1976)
	140-180 g	4.3		Sachsse & Ullmann (1975b)
Peking duck (*Anas domesticus*)	2.5-3.5 kg	2.7		Sachsse & Ullmann (1976)
	5 days (40-125 g)	1.9		Sachsse & Ullmann (1975c)
Domestic hen (*Gallus domesticus*)	5 days (40-50 g)	14		Sachsse & Ullmann (1975d)
Mallard duck (*Anas platyrhynchus*)	19 weeks (843-1357 g)	1.44		Fletcher & Pedersen (1988a)
	5 days		202*	Sachsse (1973b)
	9 days (108-120 g)		32	Fletcher & Pedersen (1988c)
Brown-headed cowbird (*Molothrus ater*)	35-55 g	85		Fletcher & Pedersen (1988b)

* Repellency recorded in all dosage groups.

decomposition, the ratio of AChE and muscarinic receptor activities remained constant at approximately 1.3:1 in normal brains, while it was always less than, or equal to, 0.5:1 after intoxication with diazinon. Normal AChE activity could be estimated from muscarinic receptor density. Parallel measurement of AChE and muscarinic receptors may assist in the postmortem diagnosis of death due to acute poisoning with anti-cholinesterase pesticide when control specimens are not available (Prijono & Leighton, 1991).

Anticholinesterases do not pass through the mother to the egg in significant amounts, but they may be deposited on the egg from the parents feathers or during pesticide application. To simulate topical exposure, fertile mallard eggs were either immersed for 30 seconds in an aqueous emulsion or single dose of an anticholinesterase in a non-toxic oil vehicle pipetted on the shell on day 3 of incubation which is a critical period with respect to organogenesis in mallards. Organophosphates were shown to be as much as 18 times more toxic when applied to the shell in an oil compared with following water immersion. Neither method of egg treatment produced teratogenicity or developmental effects at realistic pesticide application rates (Hoffman & Eastin, 1981).

A laboratory reproduction study was conducted with mallard in which birds were allowed to build their own nests and incubate eggs (Marselas et al., 1989a). Birds were fed diets containing 0, 5, 10 and 20 mg diazinon/kg diet (20 pairs per dose level). The exposure to 5 and 10 mg/kg did not result in any overt signs of toxicity or effects on reproductive performance. At 20 mg/kg, there was an increase in the number of hens that did not incubate and, although egg production was not affected, there was some reduction in the number of hatchlings and 14-day-old survivors. A companion study (Marselas et al., 1989b) with bobwhite quail was conducted at dietary concentrations of 10, 20 and 40 mg/kg. Exposures did not result in effects on reproductive performance and no mortalities or overt signs of toxicity were observed.

Henderson et al. (1994) described certain oral and dermal toxicity of diazinon to the domestic pigeon. Dose-dependent gross symptoms of organophosphorus poisoning usually appear within half an hour in pigeons dosed orally. There was a 50% inhibition of brain cholinesterase activity, i.e. ID_{50} of diazinon was about 2 mg/kg body weight. Plasma cholinesterase activity in dermally exposed birds was almost

completely inhibited by 24 h after diazinon treatment. The recovery of plasma cholinesterase after dermal exposure of pigeon was very slow.

Johnston et al. (1994) studied the interactive effects of combined treatment of red-legged partridge with diazinon and an ergosterol-biosynthesis-inhibiting (EBI) fungicide (prochloraz). Birds were pre-treated with procloraz at 180 mg/kg and then exposed to diazinon at 4.3 mg/kg 24 h later. There was a tendency to increased inhibition of cholinesterase in the plasma of treated birds but this was not significant. Synergism was significant with other organophosphorus compounds tested.

9.6.1 Field studies

Nine fairways of a golf course located in Bellingham, Washington, USA, were treated with Diazinon AG500 at a target application rate of 2.2 kg a.i./ha. The chemical application with a boomless sprayer resulted in a variable distribution of diazinon residues on the turf that ranged from 1.0 to 6.2 kg a.i./ha. The diazinon-treated turf was irrigated with 1.3 cm of water immediately following application. The post-irrigation diazinon residue levels ranged from 100 to 33 mg/kg (mean=209; SD=88; n=8). These residue levels were higher than expected based on results of turf studies in other regions of the USA. Eighty-five American wigeon died after grazing on one treated fairway on the day of application following irrigation. The brains of all 85 wigeon were analysed for acetylcholinesterase activity. Wigeon that died on the study area showed 44 to 87% depression of AChE activity when compared to controls. Upper gastrointestinal tract contents of 15 of the 85 dead wigeons contained 0.96 to 18.1 mg/kg diazinon (Kendall et al., 1992).

In the USA, use of diazinon has been discontinued on golf courses since 1988. Waterfowl often congregate near ponds on golf courses and were exposed to turf treatments. Since this restriction, deaths of grazing waterfowl (Canada geese, brent geese and American wigeon) have not occurred. Application rate reduction may also be effective in reducing risk to Canada geese, the most common grazing bird on turf. Kendall et al. (1993) closely monitored geese exposed to diazinon applied twice at 2.2 kg a.i./ha, and found no mortality despite extensive feeding on treated turf.

Hummell et al. (1992a,b,c) conducted an extensive, multi-plot assessment of the effects of turf applications of granular and liquid formulations (4.8 kg a.i./ha) of diazinon on songbirds.

Since the introduction of diazinon, sporadic mortality of waterfowl feeding on treated turf or on orchard grass has come to light in Canada. Frank et al. (1991) reported five incidents that took place in Ontario between 1986 and 1988. Fifty-seven Canada geese were poisoned by diazinon on turf sites in Ontario 1986-88. It was determined that median levels of diazinon in turf sprayed and then properly irrigated ranged from 45.4 to 256 mg/kg for a single application of 1 kg a.i./ha of the EC formulation. A value of 390 mg/kg was obtained for a single grass sample following spray at approximately 9 kg a.i./ha. Maximum residue levels for grass recovered from the oesophagi of geese killed by diazinon on turf, and collected while still fresh, ranged from 55 to 79 mg/kg.

In trials evaluating applications to large turf areas (an average of ha), survival, behaviour and reproductive performance were monitored. Smaller plots (0.09 ha) that simulated large home yards were established for granular formulations, and survival and plasma ChE were evaluated. On large plots, the liquid formulation had no effect on reproductive performance, survival or cholinesterase levels. Granular applications had a minor impact on bird population size (9.6% reduction) compared to control plots (4.8% reduction). Reproductive performance was not affected, although cholinesterase levels were reduced compared to controls. On the smaller (home-sized) turf plots there was no apparent effect on bird numbers, and plasma cholinesterase activity was not affected in any species.

Decarie et al. (1993) sprayed ornamental and other deciduous trees with diazinon at a rate of 2.2 kg a.i./ha in a suburban area of Quebec, Canada, where the compound was used to control fruit tree mites. Twelve nests of the American robin were sprayed and 65 nests untreated were used as controls. Productivity was compared between treated and control nests as was the behaviour of the birds. Mean productivity was not significantly different between the two groups. Number of feeding flights, number of female feeding flight and number of faecal sacs removed did not differ between groups but there was a significant increase in the total time spent sitting on the nest in diazinon-treated birds. The significance of this is unclear. Plasma AChE levels were reduced (993 ± 639 µg/litre in treated birds; 3585 ± 1531 µg/litre in controls), but brain AChE activity was unaffected.

10. EVALUATION OF HUMAN HEALTH RISK AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health risk

Diazinon is an organophosphorus pesticide classified by WHO as "moderately hazardous" Class II (WHO, 1996). It is absorbed from the gastrointestinal tract, through intact skin, and by inhalation. The sources of exposure to humans are occupational, accidental or through diet. Diazinon is used as a pesticide and veterinary drug to control ectoparasites. The major source of diazinon food residues in edible crops are from agricultural usage while those in meat, offal and other animal products arise from veterinary use

The results of total diet studies in the USA, United Kingdom and New Zealand suggest that levels of exposure are below the recommended Acceptable Daily Intake (ADI) of 0.002 mg/kg per day (FAO/WHO, 1994b). Diazinon is rapidly broken down, whether on plants or in animals, further reducing the risk to humans. Several different application techniques are used in applying diazinon outside and inside. Residual spraying and space treatment are often used in controlling pests indoors. Following recommended use, concentrations of diazinon detectable in the indoor air are low and do not present a health hazard. Some studies of agricultural workers have shown cases of contact dermatitis after exposure to diazinon. Toxicity studies in humans have shown that the administered daily dose of 0.025 mg/kg body weight marginally inhibits the plasma cholinesterase activity and it can be considered as the no-observed-adverse-effect level (NOAEL). Diazinon is not genotoxic and exhibits no carcinogenic potential in rats or mice. Several episodes of fatal and non-fatal accidental and suicidal poisoning have occurred. Acute poisoning causes typical cholinergic signs and symptoms. Acute pancreatitis can be associated with severe poisoning.

10.2 Evaluation for effects on the environment

The information on utilization and application rates that has been employed for this risk assessment is derived from the agricultural use of diazinon within the European Union. It should be possible to extrapolate this assessment to other agricultural uses at similar application rates elsewhere in the world. The application rates for

diazinon can be summarized as follows: arable (tractor-mounted/drawn hydraulic spray boom applications), 1.0 kg/ha; top fruit (broadcast air-assisted applications), 1.2 kg/ha.

The following risk assessment is based on the principle of calculating toxicity-exposure ratios (TERs) (Fig. 2), which follows the European and Mediterranean Plant Protection Organisation and Council of Europe (EPPO/CoE) Environmental Risk Assessment Scheme model and associated trigger values (EPPO/CoE, 1993a,b).

10.2.1 Aquatic organisms

The main risk to aquatic organisms from the use of diazinon is from spray drift during either arable applications (1.0 kg/ha) or top fruit air-assisted (1.2 kg/ha). For each of these risk scenarios, the predicted environmental concentration (PEC) in a 30-cm-deep static surface water body, arising from either arable-based spray drift at 1 m from the edge of the spray boom or from top fruit air-assisted spray drift at 3 m from the point of application (both based on Ganzelmeier et al., 1995), was calculated as follows:

$$\text{PEC (mg diazinon/litre)} = \frac{\text{max application rate (kg/ha)} \times A\ (\%\ \text{spray drift})}{300}$$

Where A = 5 for ground-based hydraulic spray application 1 m from edge of boom

= 30 for air-assisted application 3 m from point of application

10.2.1.1 Acute risk

The acute EC_{50} value for the most sensitive fish was 0.09 mg/litre and for the most sensitive aquatic invertebrate (*Gammarus*) 0.0002 mg/litre. For the most sensitive algal species the 14-day NOEC was 1 mg/litre.

(a) *Spray drift from ground-based applications:* The acute PEC for spray drift (1 m from the edge of the spray boom into a 30-cm-deep static water body at the maximum application rate (see PEC assumptions above) is 0.017 mg/litre. Therefore, the TERs, based on this PEC and the above EC_{50}/NOEC toxicity values, are: fish, 5.4; aquatic invertebrates, 0.01; and algae, 60. Based on the EPPO/CoE

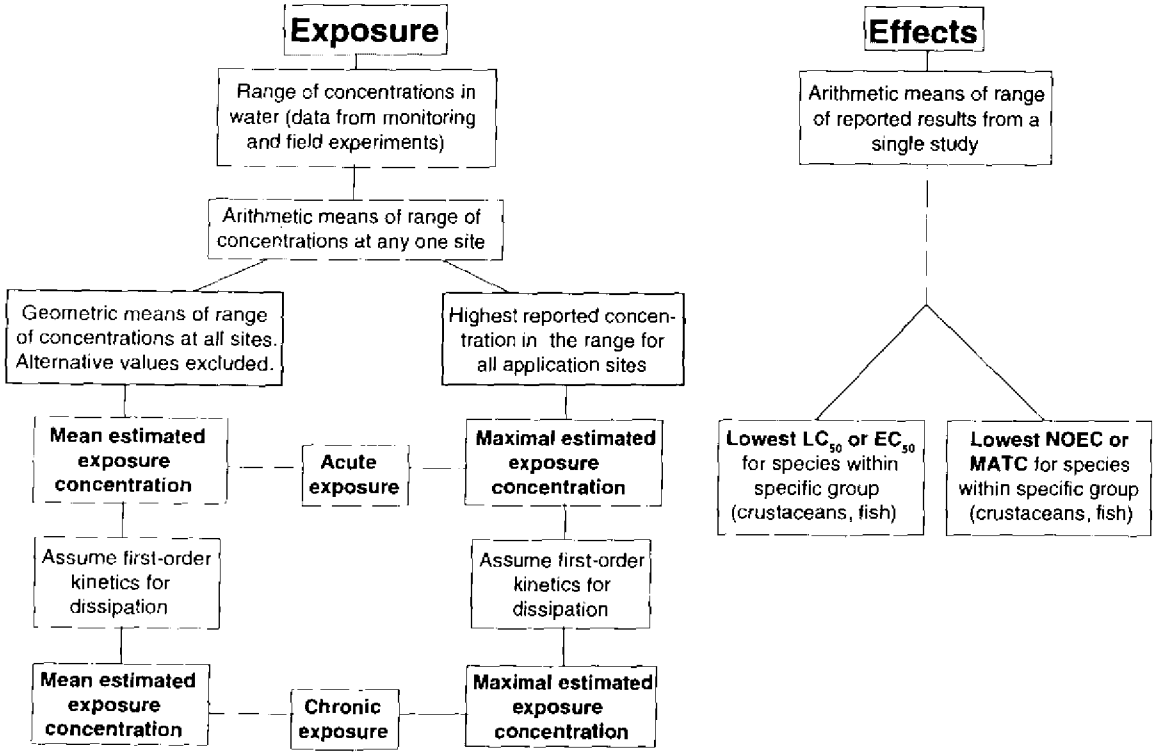


Fig. 2. Method used for deriving estimated environmental concentrations for exposure and effects

risk assessment scheme for aquatic organisms, these TERs (i.e. TERs >10 = low risk; TERs <1 = high risk) indicate a low acute risk to algae and a high risk to these organisms. The TER for fish was between 1 and 10, indicating an intermediate risk. In such risk situations the use of a "no-spray" restriction zone next to surface waters may reduce the risk to such aquatic invertebrates. For example, arable spray drift at 5 m from the edge of boom is 0.6% (Ganzelmeier et. al., 1995). Based on this 5-m drift data, the PEC is 0.002 mg/litre and results in a 5-m TER of 45 for fish. This TER at 5 m indicates that the use of a 5-m "no-spray" restriction zone next to surface waters would reduce the acute risk to fish.

(b) *Spray drift from broadcast air assisted top fruit applications:* The acute PEC for spray drift (3 m from the point of application into a 30-cm-deep static water body at the maximum application rate (see PEC assumptions above) is 0.12 mg/litre. Therefore, the TERs based on this PEC and the above EC_{50}/NOEC toxicity values are: fish, 0.75; aquatic invertebrates, 0.0017; and algae, 8.3. Based on the CoE/EPPO risk assessment scheme for aquatic organisms, these TERs indicate a high acute risk to fish and invertebrates and an intermediate risk to algae. Table 8 below summarizes the acute TERs for aquatic organisms at 1 m for arable and 3 m for broadcast air-assisted applications.

10.2.1.2 Chronic risk

There were no chronic toxicity data available.

10.2.2 Terrestrial organisms

Vertebrates are likely to be exposed to diazinon from either grazing treated vegetation or consuming contaminated insects. For this risk assessment, typical application rates of 1 kg/ha are used for ground spray application on arable crops and 1.2 kg/ha for application by air-assisted spraying for fruit

10.2.2.1 Birds

The lowest reported acute oral LD_{50} for birds is 1.1 mg/kg body weight for the Japanese quail. The dietary LC_{50} for the mallard duck is 32 mg/kg diet.

Table 8. Acute toxicity-exposure ratio (TERs) for aquatic organisms at l m for arable and 3 m for broadcast air-assisted applications

Species	EC_{50}/NOEC (mg/litre)	PEC (mg/litre) (arable)	PEC (mg/litre) (air-assisted)	TER (arable)	TER (air-assisted)
Fish (*Oncorhynchus mykiss*)	0.09	0.017	0.12	5.4	0.75
Aquatic invertebrate (*Gammarus*)	0.0002	0.017	0.12	0.012	0.0017
Algae (*Selenastrum capricornutum*)	1.0	0.017	0.12	60.0	8.3

Indicator birds for use in the risk assessment will be:

- Greylag goose *(Anser anser),* as a grazing species, with a body weight of 3 kg and total daily food consumption of 900 g vegetation (dry weight) (Owen, 1975)

- Blue tit *(Parus caeruleus),* as an insectivorous species, with a body weight of 11 g and total daily food consumption of 8.23 g (dry weight) (Kenaga, 1973).

a) *Grazing birds*

Initial residues on short grass or cereal shoots, arising from application at 1 kg/ha to arable crops, are estimated to be 112 mg/kg dry weight (based on 112 x application rate in kg/ha (EPPO/CoE, 1993a,b) and at 134.4 mg/kg from application to fruit at a rate of 1.2 kg/ha. This gives an estimated total oral intake for the goose of 100.8 and 121.0 mg for the two application rates assuming that the goose ate exclusively food contaminated at this level. This is equivalent to a daily intake of 33.6 and 40.3 mg/kg body weight, respectively. TERs can be calculated as follows:

End-point	LD_{50}/LC_{50}	Application rate (kg/ha)	Predicted concentration in food (mg/kg)	TER
Bird acute oral	1.1 mg/kg body weight Japanese quail	1 (arable)	112	0.033
		1.2 (fruit)	134.4	0.027
Bird short-term dietary	32 mg/kg diet mallard duck	1 (arable)	112	0.29
		1.2 (fruit)	134.4	0.24

The calculated TER values fall well below the EPPO/CoE trigger values for concern (TER <10) and indicate a high risk to grazing birds.

This potential risk has been confirmed in practice with reported high incidence of fatalities following application of diazinon to golf-course turf. This application is no longer recommended for this reason.

b) *Insectivorous birds*

Initial residues on small insects arising from application at 1 kg/ha to arable crops are estimated to be 29 mg/kg dry weight (based on 29 x application rate in kg/ha) (EPPO/CoE, 1993a,b) and 34.8 mg/kg from application to fruit at a rate of 1.2 kg/ha. This gives an estimated total oral intake for the blue tit of 0.24 mg and 0.29 mg for the two application rates assuming that the blue tit ate exclusively food contaminated at this level. This is equivalent to a daily intake of 21.7 and 26.0 mg/kg body weight, respectively. TERs can be calculated as follows:

End-point	LD_{50}/LC_{50}	Application rate (kg/ha)	Predicted concentration in food (mg/kg)	TER
Bird acute oral	1.1 mg/kg body weight Japanese quail	1 (arable)	29	0.05
		1.2 (fruit)	34.8	0.04
Bird short-term dietary	32 mg/kg diet mallard duck	1 (arable)	29	1.1
		1.2 (fruit)	34.8	0.92

The TERs for acute toxicity to insectivorous birds are substantially less then the trigger value of <10, indicating high acute risk to these birds. The risk factors exceed the trigger for insectivorous birds exposed short-term via the diet.

10.2.2.2 Mammals

The lowest reported acute oral LD_{50} for laboratory mammals is 82 mg/kg body weight for the mouse.

Indicator mammals for use in the risk assessment will be:

- Rabbit *(Orystolagus cuniculus)*, as a grazing mammal, with a body weight of 1200 g and a total daily food consumption of 500 g vegetation (dry weight) (Ross, personal communication to the IPCS)

- Shrew *(Sorex araneus)*, as an insectivorous mammal, with a body weight of 18 g and a total daily food consumption of 18 g (Churchfield, 1986)

a) *Grazing mammals*

Initial residues on short grass or cereal shoots arising from application at 1 kg/ha to arable crops are estimated to be 112 mg/kg dry weight (based on 112 x application rate in kg/ha) (EPPO/CoE, 1993a,b) and at 134.4 mg/kg from an application to fruit at a rate of 1.2 kg/ha. This gives an estimated total oral intake for the rabbit of 56 and 67.2 mg for the two application rates, assuming that the rabbit ate exclusively food contaminated at this level. This is equivalent to a daily intake of 46.7 and 56 mg/kg body weight, respectively. TERs can be calculated as follows:

End-point	LD_{50}	Application rate (kg/ha)	Predicted concentration in food (mg/kg)	TER
Mammal acute oral	82 mg/kg body weight mouse	1 (arable)	56	1.76
		1.2 (fruit)	67.2	1.46

This indicates a high risk to grazing mammals (trigger <10) comparable to that for grazing birds. Again, the removal of application to golf-course turf would reduce the likelihood of exposure to maximum residues of diazinon. However, grazing mammals consuming short cereal shoots could be killed following recommended use of the compound.

b) *Insectivorous mammals*

Initial residues on large insects arising from application at 1 kg/ha to arable crops are estimated to be 2.7 mg/kg dry weight (based on 2.7 x application rate in kg/ha) (EPPO/CoE, 1993a,b) and 3.24 mg/kg from an application to fruit at a rate of 1.2 kg/ha. This gives an estimated total oral intake for the shrew of 0.049 mg and 0.058 mg for the two application rates, assuming that the shrew ate exclusively food contaminated at this level. This is equivalent to a daily intake of 2.7 and 3.2 mg/kg body weight, respectively. TERs can be calculated as follows:

End-point	LD_{50}	Application rate (kg/ha)	Predicted concentration in food (mg/kg)	TER
Mammal acute oral	82 mg/kg body weight mouse	1 (arable)	2.7	30.4
		1.2 (fruit)	3.24	25.3

These TERs fall outside the trigger for high risk for insectivorous mammals but within the range for medium risk, reflecting the high acute mammalian toxicity.

10.2.2.3 Bees

The reported contact and oral toxicity to bees gives LD_{50} values of 0.22 and 0.2 µg/bee, respectively. Using application rates of 1000 and 1200 g/ha for cereals and fruit, respectively, hazard quotients are calculated to be 4545 and 5455 (application in g/ha). The trigger for concern is >50 (EPPO/CoE, 1993a,b) and, therefore, there is substantial concern for exposed bees. The compound should not be applied to flowering plants and exposure of flying bees should be avoided.

10.2.2.4 Earthworms

Earthworms are likely to be exposed to the highest concentration of diazinon following use of the granular formulation incorporated in soil at up to 2000 g/ha. Based on a soil depth of 5 cm and a soil density of 1.5 g/cm^3, the soil PEC would be 2.67 mg/kg, assuming even distribution in the medium. The reported LC_{50} for earthworms (*Eisenia foetida*) is 130 mg/kg soil, giving a TER of 48.75. As this is above the trigger value of 10 (EPPO/CoE, 1993a,b), the acute risk to earthworms should be low. Reported concentrations measured in soil are at least an order of magnitude lower than the PEC suggesting that little risk is posed to worms.

11. CONCLUSIONS AND RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT

11.1 Conclusions

The general population does not face a significant health risk from diazinon. It may cause acute poisoning in cases of over-exposure following intentional ingestion or careless handling during its manufacture and use. The general public is exposed to diazinon in the form of its residues in food, but the reported intake of diazinon is far below the acceptable daily intake. Following residual spraying and space treatment, used to control insects, the general population can be exposed to residues in the air and on surfaces. With good work practice and hygiene measures, and if safety precautions and medical surveillance are enforced, diazinon is unlikely to present a hazard to those occupationally exposed.

Diazinon does not persist in the environment and is not accumulated by organisms. It has high acute toxicity to aquatic invertebrates, fish, terrestrial birds and mammals, leading to high risk factors for many of these organisms. Field kills of waterfowl have been reported following use of the compound on amenity turf. Precautions should be taken to minimize exposure of non-target organisms (e.g., do not spray over water bodies, minimize exposure by spray drift and avoid areas where wildfowl are likely to graze).

11.2 Recommendations for protection of human health and the environment

Certain groups within the population, including agricultural workers and employees in the chemical industry, have the potential of being exposed to diazinon. Gardeners and householders may also be involved.

11.2.1 Recommendation on regulation of compound

Formulations have different classification categories: (FAO/ WHO, 1979): liquids over 20% are in category 3; other liquids or solids over 50% are in category 4; and all other solids are in category 5.

11.2.1.1 *Transport and storage*

Formulations in categories 3 and 4 should be transported and stored in clearly labelled rigid and leak-proof containers, away from containers of food and drink. Storage should be under lock and key and secure from access by unauthorized people. Formulations in category 5 should be transported and stored in clearly labelled leak-proof containers, out of reach of children and away from food and drink.

11.2.1.2 *Handling*

Protective clothing should be used by all handling of the compound. Adequate washing facilities should be available at all times during handling and should be close to the site of handling. Eating, drinking and smoking should be prohibited during handling and before washing the hands after handling.

11.2.1.3 *Disposal*

Containers may be decontaminated as recommended by the WHO Expert Committee on Vector Biology and Control on the Safe Use of Pesticides (WHO, 1991). Decontaminated containers should not be used for food and drink. Containers that are not decontaminated should be burned or crushed and buried below topsoil. Care must taken to avoid subsequent contamination of water sources.

11.2.1.4 *Selection, training and medical supervision of workers*

Pre-employment medical examination of workers is desirable. Workers suffering from active hepatic or renal disease should be excluded from contact with diazinon. Pre-employment and periodic cholinesterase test for workers is desirable especially for those handling concentrates. Training of workers in techniques to avoid contact is essential. Pilots and loaders should have special training in application methods and early symptoms of poisoning, and must wear a suitable respirator. Flagmen, if used, should wear overalls and be located well away from the dropping zone.

11.2.1.5 Labelling

Diazinon is an organophosphorus compound that inhibits cholinesterases. It is poisonous if swallowed. It may be absorbed though the skin. It is important to avoid skin contact, wear hand protection, clean protective clothing. The material must be kept out of reach of children and well away from foodstuffs, animal feed and their containers. If poisoning occurs, a physician should be called.

11.2.1.6 Residues in food

Maximum residue limits have been recommended for diazinon by the Joint FAO/WHO Meeting on Pesticides Residues (FAO/WHO, 1975).

11.2.2 Prevention of poisoning in man and emergency aid

11.2.2.1 Manufacture and formulation

Closed systems and forced ventilation may be required to reduce as much as possible the exposure of workers to diazinon.

11.2.2.2 Mixers and applicators

When mixing, protective impermeable boots, rubber apron, clean overalls and gloves should be worn. When spraying tall crops or during aerial application, a face mask should be worn, as well as an impermeable hat, clothing, boots and gloves. The applicator should avoid working in spray mist and avoid contact with the mouth. Particular care is needed when equipment is being washed after use. All protective clothing should be washed immediately after use. Splashes must be washed immediately from the skin or eyes with large quantities of water.

11.2.2.3 Other associated workers

People exposed to diazinon and associated with its application should wear protective clothing and observe the precautions described in section 11.2.2.2.

11.2.2.4 *Other populations likely to be affected*

With good application practice, other people should not be exposed to hazardous amounts of diazinon.

11.2.3 Entry into treated areas

Unprotected people should abide by re-entry periods stated on product labels.

11.2.4 Emergency aid

If symptoms appear following exposure, the person should stop work immediately, remove contaminated clothing, wash the affected skin with soap and water, if available, and flush the area with large quantities of water. If diazinon has been swallowed and the person is conscious, vomiting should be induced.

Atropine and oximes are specific antidotes and artificial respiration may be needed.

11.2.5 Surveillance test

Slight reduction of plasma cholinesterase activity can be observed. Periodic blood cholinesterase tests for workers is desirable.

12. FURTHER RESEARCH

1. Studies of exposed worker populations should be continued.

2. Diazinon should be manufactured and formulated in accordance with international specifications. It should be packed and stored under conditions that are not conducive to the formation of acutely toxic impurities.

3. The safe use of diazinon should follow label directions and precautions for handling, application and disposal.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Diazinon has been evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) on a number of occasions since 1965. An acceptable daily intake (ADI) of 0.002 mg/kg body weight has been established and maximal residues levels have been recommended for diazinon in a wide range of food commodities (FAO/WHO, 1994a,b).

The following NOAELs were established:

Rat (two-year feeding study):	1.5 mg/kg diet (0.06 mg/kg body weight per day)
Dog (one-year feeding study):	0.5 mg/kg diet (0.015 mg/kg body weight per day)
Rhesus monkey (two-year study):	0.5 mg/kg body weight per day
Human volunteers (36-day study):	0.025 mg/kg body weight per day

Diazinon has not been evaluated by the International Agency for research on Cancer (IARC).

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RÉSUMÉ ET ÉVALUATIONS

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

Le diazinon était connu jusqu'à ces dernières années sous le nom chimique de thiophosphate de di-*O*-méthyle de d'*O*-(isopropyl-2 méthyl-6 pyrimidyl-4). Selon les nouvelles conventions de nomenclature, sa dénomination chimique est désormais phosphorothioate de *O,O*-diéthyle et de *O*-2-isopropyl-6-méthylpyrimidiny-4-yle. A l'état pur, il se présente sous la forme d'un liquide incolore dégageant une légère odeur d'ester. La matière active de qualité technique est un liquide jaune à brun doté d'une odeur légère mais caractéristique. Son point d'ébullition est de 83-84 °C sous une pression de 26,6 mPa. Sa tension de vapeur (volatilité) est faible (9,7 mPa à 20 °C). Sa solubilité dans l'eau à la température ambiante est de 60 mg/litre. Le diazinon est soluble dans la plupart des solvants organiques et son coefficient de partage entre l'octanol et l'eau (log P_{ow}) est de 3,40. Il est stable en milieu neutre, mais il s' hydrolyse lentement en milieu alcalin et plus rapidement en milieu acide. Il se décompose au-dessus de 120 °C.

Il existe de nombreuses méthode d'échantillonnage et d'analyse pour le recherche et le dosage du diazinon et de ses métabolites dans différents milieux. On fait de plus en plus appel à des méthodes sensibles telles que la chromatographie en phase gazeuse, la chromatographie en phase liquide à haute performance, la spectrométrie de masse et certaines techniques immunologiques.

2. Production, usages et sources d'exposition humaine et environnementale

Le diazinon est un insecticide de contact dont le spectre d'activité est très étendu. Il est efficace contre les formes adultes et juvéniles d'insectes volants ou rampants, ainsi que contre les acariens et les arachnides. On l'utilise depuis le début des années cinquante. Il est principalement commercialisé sous la forme de concentrés émulsionnables et de poudres mouillables. Il existe également en formulations dans lesquelles il est associé à d'autres insecticides.

3. Transport, distribution et transformation dans l'environnement

La volatilisation du diazinon à partir du sol n'a qu'une importance mineure. Sa demi-vie dans la troposphère est de 1,5 h.

Le mouvement du diazinon dans le sol dépend d'un certain nombre de facteurs, en particulier de la teneur en matières organiques et en carbonate de calcium. Le diazinon ne devrait pas être très solidement fixé aux particules du sol, du fait que son K_{oc} est égal à 500 et il devrait être modérément mobile dans le sol.

La décomposition du diazinon dans le sol s'effectue principalement par voie biologique. A une température de 20 °C et pour une teneur en eau du sol égale à 60% de la capacité totale, on a constaté que dans un limon, la DT_{50} était de 5 jours. Dans des conditions stériles, et pour la même teneur en eau et la même température, on a obtenu une DT_{50} de 118 jours, ce qui donne à penser que c'est bien l'activité biologique qui est principalement responsable de la décomposition du diazinon dans le sol.

Dans les eaux naturelles, le diazinon a une demi-vie de l'ordre de 5 à 15 jours. Des processus chimiques et biologiques semblent intervenir dans sa décomposition, qui aboutit à une minéralisation en quelques semaines.

Les organismes aquatiques fixent rapidement le diazinon. On a fait état de faibles facteurs de bioconcentration chez ces organismes, allant de 3 pour la crevette à 152 pour le goujon, ce qui correspond bien à une métabolisation et à une excrétion rapides. Une demi-vie de dépuration pouvant atteindre 30 h (tissu musculaire) a été mesurée chez des poissons.

4. Concentrations dans l'environnement et exposition humaine

Le diazinon est généralement présent à faible concentration dans l'environnement. La population générale peut être exposée par voie alimentaire ou respiratoire. L'exposition par l'intermédiaire de l'eau est négligeable. En milieu professionnel, elle est principalement transcutanée.

On peut diviser les usages du diazinon en deux grandes catégories: comme pesticide en agriculture et comme médicament en médecine vétérinaire. Dans ces conditions, les résidus de diazinon présents dans les cultures vivrières résultent principalement de l'utilisation de ce composé comme pesticide en agriculture, alors que ceux qui se retrouvent dans la viande, les abats et autres produits d'origine animale proviennent de son usage comme principe actif dans certains médicaments vétérinaires.

Il n'y a que de très petites quantités de résidus dans les légumes, les fruits et les produits d'origine animale. Des études de rations totales ont montré que le composé subit une dégradation rapide dans les produits d'origine animale et végétale. On n'a pas décelé la présence de diazinon dans les échantillons d'eau de boisson analysés et sa concentration dans les eaux superficielles est de l'ordre du nanogramme par litre.

5. Cinétique et métabolisme

Le diazinon peut être résorbé dans les voies digestives, par la voie transcutanée ou après inhalation. Chez l'homme, l'absorption transcutanée est faible. Sous l'action des enzymes microsomiennes, le diazinon est oxydé en métabolites inhibant la cholinestérase comme le diazoxon, l'hydroxydiazoxon et l'hydroxydiazinon. On ne les retrouve qu'en quantités infimes dans le lait et les oeufs. Le diazinon et ses métabolites ne s'accumulent pas dans les tissus de l'organisme: une dose de diazinon administrée par voie orale est excrétée à 59-95% dans les 24 h et à 95-98% au bout de 7 jours, principalement dans les urines.

Les principales voies de dégradation métaboliques sont les suivantes:

a) Clivage du groupement ester, conduisant à des dérivés de l'hydroxypyrimidine.

b) Passage de la liaison P=S à la liaison P=O.

c) Oxydation du substituant isopropyl en alcool correspondant

d) Oxydation du substituant méthyl en alcool correspondant

e) Clivage du groupement ester sous l'action du glutathion, conduisant à un conjugué avec le glutathion.

Le clivage de l'ester phosphorique, qui conduit, directement ou par l'intermédiaire du diazoxon, aux métabolites à noyau pyrimidine, constitue l'étape principale du métabolisme du diazinon. Les métabolites qui conservent le groupement ester phosphorique sont de nature transitoire et on ne les observe qu'en petite quantité. Les métabolites sont produits en proportion et à des vitesses très variables selon les espèces. En règle générale, il n'y a pas de corrélation entre la sensibilité à l'intoxication par le diazinon et la production de diazoxon, encore qu'elle soit la plus faible chez le mouton, qui est précisément l'espèce la moins sensible. Le métabolisme extrahépatique du diazinon, en particulier l'hydrolyse du diazoxon dans le plasma, joue un rôle toxicologique plus important que le métabolisme intrahépatique, mais il est vrai que chez les oiseaux, le foie est sans doute l'organe le plus important de ce point de vue. Les métabolites qui se forment, à savoir l'acide diéthylphosphorique, l'acide diéthylthiophosphorique, et un certain nombre de dérivés contenant le noyau de la pyrimidine, sont principalement éliminés par la voie rénale.

6. *Effets sur les animaux de laboratoire et les systèmes d'épreuve* in vitro

Les améliorations apportées depuis 1979 au procédé de fabrication du diazinon ont permis de réduire sensiblement sa teneur en impuretés fortement toxiques, comme le pyrophosphate de tétraéthyle (TEPP). Grâce à ces améliorations progressives, la DL_{50} aiguë par voie orale de diazinon technique est passée, pour le rat, de 250 à 1250 mg/kg.

Quelle que soit la voie d'exposition (orale, transcutanée ou respiratoire), la toxicité aiguë du diazinon est faible. Des études à court et à long terme effectuées sur des souris, des rats, des lapins, des chiens et des singes ont montré que le seul effet préoccupant était une inhibition, liée à la dose, de l'activité acétylcholinesterasique.

Le diazinon est légèrement irritant pour la peau chez le lapin mais il n'irrite pas la muqueuse de l'oeil. Il ne provoque pas de sensibilisation cutanée. Les études toxicologiques consacrées à ses effets sur la reproduction et le développement n'ont pas mis en

évidence d'activité embryotoxique ou tératogène. La capacité de reproduction n'a pas été affectée aux doses non toxiques pour les animaux de la génération parentale. Des études de mutagénicité comportant divers points d'aboutissement *in vivo* et *in vitro* n'ont pas non plus indiqué que le diazinon soit doté d'un quelconque pouvoir mutagène. Aucun signe d'activité cancérogène n'a été relevé chez le rat et la souris. Le diazinon n'a pas provoqué pas de neuropathie retardée chez des poules. Chez des chiens et des cobayes, on a observé des cas de pancréatite aiguë ; on estime que cet effet est propre aux espèces en cause.

7. Effets sur l'Homme

On a fait état d'un certain nombre d'intoxications accidentelles ou consécutives à une tentative de suicide, qui, quelquefois, ont eu une issue mortelle. Dans certaines de ces circonstances, les troubles de nature cholinergique se sont révélés plus graves que prévu en raison de la présence d'impuretés très toxiques, comme le pyrophosphate de tétraéthyle (TEPP). On a pu aussi constater, dans certains cas, la présence d'une pancréatite aiguë réversible accompagnant le syndrome cholinergique. Cet effet s'observe également dans les intoxications par d'autres inhibiteurs de la cholinestérase. On aussi quelquefois observé un syndrome intermédiaire. Aucun cas de neuropathie retardée n'a été signalé, conformément aux données obtenues sur l'animal.. Dans tous les cas d'intoxication professionnelle dont on a eu connaissance, il y avait présence d'impuretés telles que le TEPP, le monothio-TEPP ou le sulfo-TEPP dans la formulation utilisée. Il est peu probable que les formulations actuelles contiennent encore de ces impuretés.

8. *Effets sur les autres êtres vivants au laboratoire et dans leur milieu naturel*

Le diazinon produit des effets variables sur les algues unicellulaires; on a constaté des effets d'inhibition *et* de stimulation de la croissance chez différentes espèces à des concentrations de 0,01 et de 5 mg/litre. En général, il y a réduction de la croissance au-delà de 10 mg/litre, mais dans certains cas, l'effectif de la population n'a pas été modifié à une concentration de 100 mg/litre. La rareté et la variabilité des données rendent difficile l'évaluation des effets produits sur les autres microorganismes.

Les valeurs de la CL_{50} à 96 h (effets aigus) pour les invertébrés aquatiques vont de 0,2 dans le cas de *Gammarus fasciatus* à 4,0 mg/litre pour la crevette *Hyallela azteca*. Les mollusques sont notablement moins sensibles, d'après une épreuve effectuée sur le gastéropode *Gillia attilis*. Des effets sublétaux ont été observés au niveau du comportement à des concentrations comprises entre 0,1 et 0,01 mg/litre.

Les valeurs de la CL_{50} (effets aigus) pour les poissons varient de 0,09 mg/litre chez la truite arc-en-ciel (*Oncorhynchus mykiss*) à 3,1 mg/litre chez le poisson-chat (*Channa punctatus*). Chez les stades juvéniles des poissons, il y a inhibition de la croissance aux concentrations comprises entre 0,01 et 0,2 mg/litre. Une exposition aiguë au diazinon provoque la suppression de l'activité acétylcholinestérase cérébrale.

Pour le lombric *Eisenia foetida*, la CL_{50} dans le sol est de 130 mg/kg de terre.

Chez les oiseaux, la toxicité aiguë par voie orale (DL_{50}) varie de 1,1 mg/kg p.c. pour la caille japonaise à 85 mg/kg p.c. pour le molothre des troupeaux. Les valeurs de la CL_{50} obtenues lors d'études d'alimentation, vont de 32 mg/kg de nourriture chez le colvert à 900 mg/kg de nourriture chez la caille japonaise (on observe un effet répulsif à ces doses élevées). Des études de rations alimentaires en laboratoire ont montré que la dose sans effet nocif observable sur la reproduction des oiseaux était égale à 20 mg/kg de nourriture chez le colvert et à 40 mg/kg de nourriture chez le colin de Virginie. Après ingestion, il y a inhibition de l'acétylcholinesterase cérébrale. Le diazinon peut également pénétrer par voie transcutanée. On a signalé une mortalité importante chez du gibier d'eau à la suite de pulvérisations de diazinon sur du gazon. Des études de terrain au cours desquelles on a épandu du diazinon à raison de 4,8 kg de matière active par hectare, ont montré qu'il n'en résultait aucune mortalité pour les oiseaux chanteurs. L'épandage de granulés a provoqué une légère réduction des populations d'oiseaux chanteurs par rapport aux populations témoins. Les études de laboratoire montrent que l'ingestion d'un petit nombre de granulés peut être fatale à un oiseau de petite taille.

RESUMEN Y EVALUACIONES

1. Identidad, propiedades físicas y químicas y métodos analíticos

El nombre químico del diazinon es *O,O*-dietilo *O*-2-isopropil-6-metilpirimidinil-4-yl fosforotioato. La sustancia pura forma un líquido incoloro con un ligero olor a éster. El principio activo de calidad técnica es un líquido amarillo pardusco con un ligero olor característico del compuesto. Su punto de ebullición es de 83-84 °C a 26,6 mPa y su presión de vapor (volatilidad) es baja (9,7 mPa a 20 °C). Su solubilidad en agua a temperatura ambiente es de 60 mg/litro. El diazinon es soluble en la mayoría de los disolventes orgánicos y tiene un coeficiente de reparto octanol/agua (log P_{ow}) de 3,40. Es estable en medios neutros, pero se hidroliza lentamente en medios alcalinos y más rápidamente en medios ácidos. Se descompone a temperaturas superiores a los 120 °C.

Se ha desarrollado un gran número de métodos de muestreo de análisis para la determinación del diazinon y sus metabolitos en distintos medios. Cada vez se utilizan más los métodos sensibles, tales como la cromatografía de gases, la cromatografía líquida de alta resolución, la espectrometría de masas y el inmunoensayo.

2. Producción, usos y fuentes de exposición humana y ambiental

El diazinon es un insecticida organofosforado de contacto, con una actividad insecticida de amplio espectro. Es eficaz contra las formas adultas y juveniles de insectos, voladores o no, ácaros y arañas. Se utiliza desde principios del decenio de 1950. El diazinon se prepara principalmente en forma de polvos humectables y concentrados emulsionables. También se encuentra en preparaciones mixtas combinado con otros insecticidas.

3. Transporte, distribución y transformación en el medio ambiente

La volatilización del diazinon en el suelo es de poca magnitud. El diazinon tiene una semivida troposférica de 1,5 horas.

Su movilidad en el suelo depende en gran medida de una serie de factores, en particular de la materia orgánica y del contenido en carbonato de calcio. Su K_{oc} de 500 no da lugar a prever una fijación fuerte a las partículas del suelo, sino a una movilidad moderada en el suelo.

Los procesos biológicos parecen ser el factor principal en la degradación del diazinon en el suelo. A 20 °C y con un contenido de humedad del suelo del 60% de la capacidad de campo en un suelo franco limoso, el TD_{50} fue de 5 días. En condiciones de esterilidad a 20 °C y con un 60% de capacidad de campo, el TD_{50} fue de 118 días, lo que parece indicar que la actividad geológica es la principal responsable de la degradación en el suelo.

En el agua presente en la naturaleza, el diazinon tiene una semivida de 5 a 15 días. Al parecer, en la degradación del diazinon intervienen procesos tanto químicos como biológicos que dan lugar a la mineralización al cabo de pocas semanas.

La absorción del diazinon por los organismos acuáticos es rápida. Con respecto a los organismos acuáticos, se han señalado factores de bioconcentración bajos que oscilan entre 3 en el caso del camarón y 152 en el caso del gobio, lo que parece indicar un metabolismo y una eliminación rápidos. Se han notificado semividas de depuración en los peces de hasta 30 horas (mejillón).

4. Niveles medioambientales y exposición humana

Los niveles medioambientales de diazinon son generalmente bajos. Las vías de exposición de la población general son la inhalación y la alimentación. La exposición a través del agua es mínima. La exposición profesional es fundamentalmente cutánea.

Los usos del diazinon se pueden clasificar en dos categorías principales, a saber, como plaguicida en la agricultura y como fármaco en la medicina veterinaria. Por consiguiente, la presencia de residuos de diazinon en los cultivos comestibles obedece principalmente a su utilización como plaguicida agrícola, mientras que su presencia en la carne, los despojos y otros productos de origen animal se debe a su utilización como fármaco de uso veterinario que contiene el principio activo.

Los residuos de diazinon presentes en verduras, hortalizas, frutas y productos de origen animal son muy escasos. Los resultados de estudios realizados sobre dietas totales dan a entender que el diazinon se degrada rápidamente tanto en los productos de origen vegetal como en los de origen animal. No se ha detectado la presencia de diazinon en muestras de agua potable y su concentración en aguas de superficie se sitúa en niveles de ng/litro.

5. Cinética y metabolismo

El diazinon se puede absorber por el aparato digestivo, a través de la piel intacta y tras su inhalación. La absorción transcutánea en el ser humano es baja. Las enzimas microsómices oxidan el diazinon produciendo metabolitos inhibidores de la colinesterasa, tales como el diazoxón, el hidroxidiazoxón y el hidroxidiazinon. Sólo se detectan cantidades mínimas de metabolitos en la leche y los huevos. El diazinon y sus metabolitos no se acumulan en los tejidos corporales; el 59-95% de una dosis oral de diazinon se excreta en un plazo de 24 horas y el 95-98% se excreta en un plazo de 7 días, principalmente por orina.

Las principales vías metabólicas de degradación del diazinon son las siguientes:

a) Ruptura del enlace de éster, que da lugar a los derivados de la hidroxipirimidina.

b) Transformación de la fracción P-S en el derivado P-O.

c) Oxidación del sustituyente isopropílico, que da lugar a los correspondientes derivados alcohólicos terciarios y primarios.

d) Oxidación del sustituyente metílico, que da lugar al alcohol correspondiente.

e) Ruptura del enlace éster mediada por el glutatión, que da lugar a un conjugado de glutatión.

La ruptura del enlace éster fosfato, que da lugar, directamente o por vía del diazoxón, al metabolito pirimidílico, desempeña una función determinante en el metabolismo del diazinon. Los metabolitos

que mantienen el enlace éster fosfato son de carácter transitorio y sólo se han detectado en pequeñas cantidades. La cantidad de metabolitos y su velocidad de producción varían ampliamente de una especie a otra. En general, la producción de diazoxón no está relacionada con la sensibilidad a la intoxicación por diazinon, si bien es más baja en la especie menos vulnerable, los ovinos. El metabolismo extrahepático del diazinon, en especial la hidrólisis del diazoxón en el plasma, es toxicológicamente más importante que el metabolismo hepático, pero este último probablemente sea el más importante en las especies aviarias. Los metabolitos formados, esto es, el ácido dietilfosfórico, el ácido dietiltiofosfórico y los derivados del anillo pirimidinílico, se eliminan principalmente por los riñones.

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

Las mejoras introducidas en la fabricación del diazinon desde 1979 han reducido significativamente su contenido de impurezas sumamente tóxicas, como por ejemplo el pirofosfato de tetraetilo (TEPP). Como resultado de estas mejoras progresivas, la DL_{50} aguda por vía oral del diazinon de calidad técnica ha aumentado (por ejemplo, de 250 mg/kg a 1250 mg/kg en la rata).

La toxicidad aguda por vía oral o cutánea o por inhalación es baja. Los estudios a corto y largo plazo efectuados en ratones, ratas, conejos, perros y monos han puesto de manifiesto que el único efecto preocupante es la inhibición de la actividad de la acetilcolinesterasa, relacionada con la dosis.

En el conejo, el diazinon ocasiona una ligera irritación de la piel, pero no de los ojos. El diazinon no sensibiliza la piel. Los estudios de reproducción y desarrollo no han revelado indicios de potencial embriotóxico ni teratogénico. No se detectaron efectos en el proceso de reproducción tras la administración de dosis que no eran tóxicas para los animales progenitores. Los estudios de mutagenicidad con distintas variables de valoración *in vivo* y *in vitro* no revelaron un potencial mutagénico. No hay indicios de carcinogenicidad en ratas ni en ratones. El diazinon no causa neuropatía retardada en las gallinas. Se ha señalado que el diazinon provoca pancreatitis aguda en perros y cobayos; se considera que se trata de un efecto específico de determinadas especies.

7. Efectos en el ser humano

Se han señalado varios casos de intoxicación accidental o suicida con diazinon, algunos de los cuales fueron mortales. En algunos de ellos, el síndrome colinérgico puede haber sido más grave de lo previsto debido a la presencia de impurezas sumamente tóxicas, tales como el TEPP. En algunos casos se produjeron pancreatitis agudas reversibles asociadas a un síndrome colinérgico grave. Eso se produce también tras la intoxicación con otros inhibidores de la colinesterasa. En varios casos también se detectó el síndrome intermedio. No se ha señalado ningún caso de neuropatía retardada, como es de prever según los datos dimanantes de estudios realizados en animales. Los casos notificados de intoxicación tras una exposición profesional siempre han ido asociados a la presencia de impurezas en la formulación, tales como el TEPP, el monotio-TEPP o el sulfo-TEPP. Es poco probable que se encuentren estas impurezas en las formulaciones disponibles en la actualidad.

8. Efectos en otros organismos en el laboratorio y en el medio ambiente

Los efectos del diazinon en las algas unicelulares son variables; se ha señalado tanto la inhibición como la estimulación del crecimiento en distintas especies, con concentraciones de 0,01 a 5 mg/litro. En términos generales, las tasas de crecimiento disminuyen con concentraciones superiores a 10 mg/litro, si bien en algunos casos el tamaño de la población puede permanecer invariable con concentraciones de 100 mg/litro. La escasez y variabilidad de los datos dificulta la evaluación de los efectos sobre otros microorganismos.

En pruebas realizadas a las 96-h, la CL_{50} aguda para los invertebrados acuáticos oscilaba entre 0,2 mg/litro en *Gammarus fasciatus* y 4,0 mg/litro en camarones *(Hyallela azteca)*. Según una prueba única a la que se sometió a *Gillia attilis*, los moluscos son sustancialmente menos sensibles. Se han señalado efectos subletales en el comportamiento con concentraciones de 0,1 a 0,01 mg/litro.

La CL_{50} aguda para los peces oscila entre 0,09 mg/litro para la trucha arco iris *(Oncorhynchus mykiss)* y 3,1 mg/litro para el bagre (*Channa punctatus*). El crecimiento durante las primeras fases de la vida de los peces se inhibía con concentraciones de 0,01 a 0,2 mg/litro.

La actividad de la acetilcolinesterasa cerebral se inhibe tras una fuerte exposición al diazinon.

La CL_{50} en el suelo para la lombriz de tierra *(Eisenia foetida)* es de 130 mg/kg de suelo.

La toxicidad aguda por vía oral (DL_{50}) en las aves varía entre 1,1 mg/kg de peso corporal para la codorniz japonesa y 85 mg/kg de peso corporal para aves del género *Molothrus*. Los valores de la CL_{50} en la alimentación oscilan entre 32 mg/kg de alimentos en el pato silvestre y 900 mg/kg de alimentos en la codorniz japonesa (se detectó repelencia con estas altas concentraciones en la alimentación). En estudios de laboratorio realizados en aves, la concentración de diazinon en la dieta sin efectos observados en la reproducción era de 20 mg/kg de alimentos en el pato silvestre y de 40 mg/kg de alimentos en la codorniz (*Colinus virginianus*). La actividad de la acetilcolinesterasa cerebral se inhibe tras la ingestión. El diazinon también se puede absorber por vía cutánea. Se ha notificado una considerable mortandad de las aves acuáticas en la naturaleza, tras la aplicación de diazinon al césped. En estudios sobre el terreno en que se aplicaron formulaciones líquidas al césped con una concentración de 4,8 kg ai/ha no se registró mortalidad ni se produjeron efectos sobre la reproducción de las aves canoras. La aplicación en forma de gránulos provocó una pequeña reducción en el tamaño poblacional de aves canoras, en comparación con el grupo testigo. La ingestión de pequeñas cantidades de gránulos puede resultar mortal para las aves pequeñas, como se ha demostrado en estudios de laboratorio.

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