The Reconsideration of Registrations of Products containing Diazinon and their Labels

Part 1 Product Cancellations

REVIEW REPORT

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FOREWORD

The APVMA is the National Registration Authority for Agricultural and Veterinary Chemicals. For information regarding the APVMA, please visit www.apvma.gov.au.

The APVMA is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the *Agricultural and Veterinary Chemicals Code Act, 1994* (Agvet Codes).

The APVMA can reconsider the approval of active constituents, the registration of chemical products or the approval of labels for containers of chemical products at any time. This is outlined in Part 2, Division 4 of the Agvet Codes.

The basis for the reconsideration is whether the APVMA is satisfied:

- that the continued use of the products will not pose an unacceptable risk to people, the environment or trade;
- that the products are effective for the purposes claimed; and
- that the product labels contain adequate instructions.

A reconsideration may be initiated when new research or evidence has raised concerns about the use or safety of a particular chemical, a product or its label.

The process for reconsideration includes a call for information from a variety of sources, a review of that information and, following public consultation, a decision about the future use of the chemical or product.

In undertaking reviews, the APVMA works in close cooperation with advisory agencies including the Department of Health and Aging, Environment Australia, the National Occupational Health and Safety Commission, and State Departments of Agriculture as well as other expert advisors, as appropriate.

The APVMA has a policy of encouraging openness and transparency in its activities and community involvement in decision-making. The publication of review reports is a part of that process.

The APVMA also makes these reports available to the regulatory agencies of other countries as part of bilateral agreements or as part of the OECD *ad hoc* exchange program. Under this program it is proposed that countries receiving these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.

This document is Part 1 of '*The Reconsideration of Approvals and Registrations of Products containing Diazinon*' and relates to products containing diazinon that are unstabilised hydrocarbon-based formulations and products containing diazinon that are used as dog and kennel flea treatments. The review's findings and recommendations are based on information collected from a variety of sources, including data packages and information submitted by registrants, information submitted by members of the public including user groups, questionnaires sent to key user/industry groups and government organisations, and literature searches.

The information and technical data required by the APVMA to review the safety of both new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken. Details of the APVMA's data requirements for registration are outlined in various publications, which can be purchased or obtained by contacting the APVMA. Among these are the APVMA's *Guidelines for Registering Agricultural/Veterinary Chemicals.*

The draft review report containing the APVMA's preliminary assessments (The NRA Review of Diazinon, Volume I) and the technical reports from its advisory agencies (Volume II) for all registrations and approvals relating to diazinon are available from the APVMA website http://www.apvma.gov.au/chemrev/chemrev.shtml. Copies can also be obtained by contacting:

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ABBREVIATIONS AND ACRONYMS

µg	microgram
ANZECC	Australia & New Zealand Environment and Conservation Council
APVMA	Australian Pesticides & Veterinary Medicines Authority
ai	active ingredient
DT_{50}	time required for 50% of a chemical to degrade
EC	emulsifiable concentrate
EC_{50}	concentration at which 50% of the test population are affected
h	hour
ha	hectare
IPM	integrated pest management
kg	kilogram
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
ME	microencapsulated
mg	milligram
MRL	maximum residue limit
OP	organophosphorus pesticide
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
US EPA	United States Environment Protection Agency

EXECUTIVE SUMMARY

Introduction

Diazinon is an organophosphorus insecticide and acaricide used in the control of sucking and chewing insects and mites in a range of situations. Diazinon has been widely used for many years in ectoparasiticide formulations for sheep and cattle and in collars and washes for external parasite control in companion animals. It is also used in agriculture and horticulture for control of insects in crops, ornamentals, lawns, fruit and vegetables and as a pesticide in domestic, agricultural and public buildings.

A review of all existing registrations and approvals relating to the broad-spectrum organophosphorus insecticide diazinon was commenced in 1996. The reason for review was concern about the potential for diazinon to form highly toxic breakdown products, particularly if the chemical is exposed to a small amount of water. Other concerns were in respect of public health, the environment and trade.

Information collected from a variety of sources, including data packages and information submitted by the approval holders and registrants, information submitted by members of the public including user/industry groups and government organizations and literature searches was reviewed. Review findings in the form of a draft report were released for public comment in August 2000. A revised report was released in August 2002 in response to additional information and comments received.

Draft review findings are that active and most formulation types are manufactured in such a way as to mitigate risk of formation of toxic breakdown products during storage or use. Information is still being assessed to determine other safety aspects. However some liquid formulations, specifically those that are based on hydrocarbon solvent and that do not contain adequate stabiliser, have the potential to form toxic breakdown products. They are considered to be a risk to public health and cancellation of product is recommended. In addition liquid formulations used in the domestic setting as dog and kennel treatments are considered to present a risk to the environment and cancellation is recommended.

This report is Part 1 of *'The Reconsideration of Registrations of Products containing Diazinon and their Labels'* and relates to products containing diazinon that are unstabilised hydrocarbon-based formulations and products containing diazinon that are used as dog and kennel flea treatments.

Chemistry findings relevant to product cancellations

The chemistry assessment highlighted the potential for some liquid formulations, specifically those that are based on hydrocarbon solvent and that do not contain adequate stabiliser to have the potential to form toxic breakdown products. These toxic impurities could pose risks to both target animals and users but formation of these breakdown products can be prevented if formulations containing diazinon also contain adequate stabiliser.

In addition to other cholinesterase-inhibiting metabolites of diazinon the phosphate breakdown products of diazinon can combine to form the highly toxic compounds O,O-TEPP, O,S-TEPP (monotepp) and S,S-TEPP (sulfotepp) under the catalytic influence of other by-products in the presence of trace amounts of water.

Compared to the parent diazinon, sulfotepp and monotepp are 300-fold and 2500-fold more toxic, respectively. To stabilise the active diazinon, epoxidised soybean oil is added and has successfully reduced the formation of toxic contaminants in the active material. APVMA approved sources of diazinon are stabilised with epoxidised soybean oil.

However, there are concerns that the level of stabiliser in formulated products that are hydrocarbon-based, including emulsifiable concentrates, may be insufficient to reliably prevent the formation of the toxic impurities. In 1994, a survey of common diazinon emulsifiable concentrate formulations was conducted with products that are readily available from retail outlets throughout Australia. This survey found that about 15% of the products (26 out of 169) contained degradation products at levels that exceeded the allowable limits.

Regulatory action was taken by the APVMA after the 1994 survey to remove non-compliant products from the market, but there have been poisoning incidents reported since that time, usually associated with dog wash or ectoparasiticide products that had exceeded their use-by date. The presence of toxic degradation products following unsuitable storage conditions in hydrocarbon-based/emulsifiable concentrate diazinon products is considered to be the likely cause of reported cases of fatal companion animal, cattle intoxications and occupational hazards attributed to diazinon.

The chemistry assessment concluded that products containing diazinon that are based on hydrocarbon solvents formulated without adequate stabiliser are considered to be a risk to public health and animal safety.

Environmental Findings related to product cancellations

Assessment of the environmental chemistry and fate of diazinon showed that it is degradable in most environments and it is not expected to bioaccumulate or leach to a significant extent. The principal metabolite of diazinon is more stable and mobile in soils than diazinon itself and it could leach in soils that are prone to leaching. Diazinon is slightly volatile from leaves and other surfaces but diazinon vapours are not expected to persist in the air.

Diazinon is toxic to most organisms and in particular to aquatic invertebrates. The hazard to bees was found to be high, particularly from direct application. There is also a possible hazard to soil invertebrates but no toxicity data were provided for these organisms.

Diazinon has been detected in sewage effluent in the Sydney region and this appears to be linked to use of companion animal products. Proposals to restrict domestic hydrocarbon based/emulsifiable concentrate products to those that contain stabiliser are not expected to significantly reduce this problem. Levels are well above ANZECC water quality guidelines and at many times during the year the river flow is insufficiently high to allow adequate dilution to occur. Safe disposal of used dogwash water on the garden lawn/soil is not acceptable on health grounds and is not practical for dogs washed in laundry tubs. Particular concerns arise in urban areas. Use of companion animal products appears to give rise to excessive concentrations in sewage effluent in the Sydney region and probably in other cities. As this cannot be dealt with by the inclusion of appropriate label statements, it is concluded that continued use of products containing diazinon that are dog and kennel flea treatments may have a harmful effect on the environment.

Recommendations

Based on the information assessed and as outlined in this report, the APVMA cannot be satisfied that the continued use, or any dealing with products containing diazinon that are unstabilised hydrocarbon-based formulations in accordance with the recommendations for use:

- would not be an undue hazard to the safety of people exposed to them during their handling;
- would not be likely to have an effect that is harmful to human beings; and, for products used on animals
- would not be likely to have an unintended effect that is harmful to animals.

The APVMA has therefore recommended cancellation of these products.

The APVMA also cannot be satisfied that the continued use or any dealing with product containing diazinon that are dog and kennel flea treatments:

- would not be likely to have an unintended effect that is harmful to the environment.

The APVMA has therefore recommended cancellation of these products.

1. REASONS AND SCOPE OF THE REVIEW

1.1 Current use of diazinon in Australia

Diazinon is a broad-spectrum organophosphate insecticide that has been registered for use in Australia for over 30 years. It has been widely used for many years in ectoparasiticide formulations for sheep and cattle and in collars and washes for external parasite control in companion animals. It is also used in agriculture and horticulture for control of insects in crops, ornamentals, lawns, fruit and vegetables and as a pesticide in domestic, agricultural and public buildings.

Diazinon products registered in Australia include a number of different formulation types including dusts and powders, hydrocarbon-based/emulsifiable concentrates, microencapsulated formulations, water based liquid formulations, flea collars and ear tags. Some products may also contain other actives with insecticidal properties.

1.2 Reasons for the reconsideration of registration and approvals related to diazinon

The decision to review actives and products containing diazinon stems from concerns about public health, occupational health and safety, residues, trade and the environment. In summary, the concerns over the chemical were:

- reported incidents of human poisoning;
- potential acute toxicity risk;
- possible long-term effects on users exposed to diazinon over a period of time;
- detection of toxic breakdown products in registered products;
- reported incidents of animal fatalities;
- ground water contamination;
- reported incidents of bird kills in Australia;
- US Environment Protection Agency (US EPA) regulatory action to partially restrict uses based on its toxicity to birds and aquatic species;
- lack of appropriate maximum residue limits (MRLs) for agricultural and horticultural uses;
- residue detections in export produce above MRLs;
- MRL inconsistencies with major trading partners (US, Canada, Codex).

1.3 Overseas Regulatory Status

Diazinon is registered for use on many commodities in a number of countries throughout the world, including Finland, Denmark, Ireland, UK, Belgium, Greece, US, India, Sweden, The Netherlands, Austria, France, Spain, Italy, Japan, China, Brazil and Portugal. To date, no information has been discovered which suggests that action has been taken in any country to place a total ban on this chemical, although limitations in certain use situations have been imposed.

The US EPA has undertaken a review of diazinon culminating in an as an Interim Reregistration Eligibility Decision. As part of the diazinon interim decision all registrations of product for indoor and outdoor residential use of diazinon will be 'phased out and cancelled by December 2004'. This is a voluntary regulatory approach based on the decision of registrants to withdraw from the market rather than address identified concerns. The US EPA has not determined that these uses are unsafe. A wide range of agricultural uses will continue in the US, including use of diazinon on fruit and vegetable crops including mushrooms, onions, bananas and pineapples. The US EPA is currently conducting a cumulative evaluation of organophosphorous pesticides.

In the UK diazinon is being progressively phased out because of a lack of data to support continued use. The situation is similar at the European Union level and this is likely to lead to the progressive withdrawal of diazinon from use in Europe.

There has also been regulatory activity in relation to diazinon in India where its use on plant hoppers in rice has been cancelled because use results in adverse effects on brown planthopper predators.

There has been no move overseas to withdraw import tolerances for diazinon nor is such a move anticipated. To date, overseas regulatory activity on diazinon has not affected Australia's trade with other countries.

1.4 Scope of the review

The review covered all aspects of the registrations and approvals relating to diazinon. Assessments considered the active approval, product registrations and use patterns in terms of the impact on public health, occupation health and safety, the environment and trade.

1.5 Scope of this review report

This document relates only to products containing diazinon that are unstabilised hydrocarbon-based formulations and products containing diazinon that are used as dog and kennel flea treatments.

The products subject to this part of the review are listed in Table 1 and 2. Note that many product registrations originally included in the review have either not been renewed or have been voluntarily cancelled. Product registrations since the commencement of the review, while not formally part of the review, are registered on the condition that they comply with the outcomes of the review. The new product registrations are not listed in the tables.

Table 1 Products containing diazinon that are unstabilised hydrocarbon-based formulations

Product number	Product name	Registrant	Label approval number(s)
31960	Hortico Ant Killer Spray Insecticide	Hortico (Aust) Pty Ltd	Ψ 31960/0700
41307	Hortico Lawn Grub & Insect Killer	Hortico (Aust) Pty Ltd	Ψ 41307/0800
41783	Diazol Sheep Dip, Jetting Fluid and Blowfly Dressing	Makhteshim-Agan (Aust) Pty Ltd	Ψ

Table 2 Products containing diazinon that are used as dog and kennel flea treatments

Product number	Product name	Registrant	Label approval number(s)
40019	Gammawash D Insecticidal Dog Wash	Wesfarmers Landmark Limited	Ψ
40653	Exelpet Yard and Kennel Flea Control Concentrate	Exelpet Products (a division of Effem Foods Pty Ltd)	Ψ 40653/1197
49853	Nucidol 200 Dog Wash	Novartis Animal Health Australasia Pty Ltd	49853/01 49853/0498

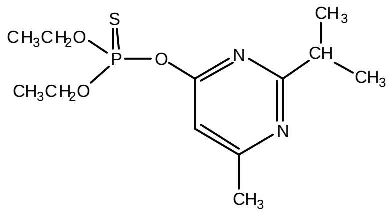
Ψ Label transitioned from the States and so not having an approval number.

2. CHEMISTRY ASSESSMENT

Diazinon is an organophosphorus insecticide classified by WHO as “moderately hazardous” Class II. It has a wide range of insecticidal activity and is effective against adult and juvenile forms of flying insects, crawling insects, acarians and spiders. It is used widely to control insects of agricultural and public health significance.

2.1 Identification of the Substance

Common name:	Diazinon (ISO, SA)
IUPAC name:	O,O-diethyl O-(2-isopropyl-6-methylpyrimidin-4-yl) phosphorothioate
CA name:	O,O-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] phosphorothioate
CAS Registry number:	333-41-5
Chemical formula:	$C_{12}H_{21}N_2O_3PS$
Molecular weight:	304.3
Chemical structure:	



Primary use:	Insecticide
Secondary use:	Ectoparasiticide
Chemical group:	Organophosphorus compound
Synopsis:	An organophosphorus pesticide of moderate mammalian toxicity.
Absorption route:	It may be absorbed by all routes of exposure. May be absorbed by the intact skin as well as by inhalation and from gastrointestinal tract.
Mode of action:	Cholinesterase inhibition after conversion to the oxygen analogue, diazoxon.

2.2 Physical and Chemical Properties of the Pure Active Constituent

Colour	Clear, colourless
Odour	Faint ester-like odour
Physical state	Viscous liquid
Boiling point	83-84 ^{o}C at 0.0002 mm Hg (26.6 Pa); 125 ^{o}C at 0.001 mm Hg (133 mPa)
Octanol/water partition coefficient (Log P)	3.30 (Novartis; WHO, 1998); 3.42 (Nippon Kayaku)
Vapour pressure	1.4 x 10^{-4} mmHg at 20 ^{o}C;

	2.8×10^{-4} mmHg at 25 ^oC
Refractive index ($_nD^{20}$)	1.4978-1.4981 (20 ^oC)
Volatility (at 20 ^oC)	2.3 mg/m^3
pH at 20 ^oC	Approximately 6.0
Solubility in water	40 mg/L at 20 ^oC (Novartis); 60 mg/L at 20 ^oC (WHO, 1998)
Solvent solubility (at 20 ^oC)	Completely miscible in acetone, methanol, ethanol, chloroform, acetonitrile, cyclohexane, dichloromethane, hexane, benzene, petroleum ether, and carbon disulfide
Specific gravity at 20 ^oC	1.116-1.118
Viscosity at 20 ^oC	13 mPa.s
Stability	Diazinon decomposes at temperatures above 120^{0}C. It is stable in alkaline media, but is slowly hydrolysed by water and by dilute acids [it is quite stable in the pH range of 6.0 to 8.0, although the hydrolysis process is quite rapid under acidic ($pH < 3.1$) or alkaline conditions ($pH > 10.4$)]. The presence of a small amount of water in acid medium promotes decomposition to highly toxic by-products.
Hydrolysis	At pH 5, $t_{½}$ = 38 days; at pH 7, $t_{½}$ = 78 days; and at pH 9, $t_{½}$ = 40 days (Novartis, 1972)
Photolysis	When an aqueous solution of 34 mg/L diazinon was exposed to artificial sunlight, 53% decomposition had occurred after 97 hours (Novartis, 1979)
Corrosiveness	Diazinon is considered non-corrosive

2.3 Physical and Chemical Properties of the Diazinon Source Material

Colour	Clear yellow to brown
Odour	Faint ester-like odour
Physical state	Slightly viscous liquid
Octanol/water partition coefficient (Log P)	3.30
Water solubility (at 20 ^oC)	Approximately 40 to 60 mg/L (based on the pure active substance)
Solvent solubility	As per the pure active substance
Density	As per the pure active substance
Vapour pressure	The vapour pressure of the active ingredient is 1.4×10^{-4} mmHg at 20 ^oC
Volatility	2.4 mg/m^3 at 20^{0}C and 17.6 mg/m^3 at 40^{0}C;
Stability	As per the pure active substance
Viscosity (at 20 ^oC)	13 to 14 mPa.s (Novartis)
Hydrolysis (at 20 ^oC)	pH 3.1, $t_{½}$ = 11.8 hours
Flammability	The flashpoint is over 170 ^oC by open cup
Ignition temperature	360 ^oC

Suitable extinguishing agent	Powder, foam, CO_2, or water sprays (do not use direct jet of water). Combustion products are toxic and/or irritant.
Explosiveness	Not explosive
Hazard rating	Health hazard – high Occupational toxicity – high Fire hazard – fumes would be expected to be moderately to highly toxic

2.4 Scheduling

Diazinon is included in Schedule 6 of the SUSDP except for dust preparations containing 2% or less of diazinon (Schedule 5).

2.5 Approved Sources of Diazinon

The approved sources of diazinon affected by this review are listed below:

Approval No	Company	Manufacturing site
44033	Makhteshim-Agan (Australia) Pty Ltd	Makhteshim Chemical Works Ltd New Industrial Estate Beer-Sheva 84100 ISRAEL
44289, 44290, 44291 (MC)*	Novartis Animal Health Australasia Pty Limited	Ciba-Geigy Corporation McIntosh Plant Geigy Road McIntosh Alabama 36553 USA
46132	Tomen Australia Limited	Nippon Kayaku Co., Ltd Kashima Factory 6-Sunayama, Hasaki-Machi Kashima-Gun, Ibaraki-pref. JAPAN

*MC is manufacturing concentrate

All sources of diazinon approved by the NRA are stabilised with epoxidised soybean oil to prevent the formation of toxic degradation products (see under stability and effect of aging on the acute toxicity). It should be noted that the formulated products must be manufactured using approved source material only.

2.6 Formulations

Products registered in Australia include a number of different formulations, including dust, (20-40 g/kg), emulsifiable concentrate (3-800 g/L), microencapsulated (240-270 g/L), aqueous liquid (38-500 g/L), flea collars (150-168 g/kg), insecticidal powders (15-37.5 g/kg) and cattle ear tags (240-300 g/kg). Some products may also contain other actives with insecticidal properties.

2.7 NRA Minimum Compositional Standard/FAO Specification for Diazinon Technical

Note: Diazinon Technical, or source material, refers to the grade or purity of active constituent that is used to formulate products containing diazinon.

Active ingredient: (calculated on a dry weight, solvent and stabiliser free basis).	Not less than 950 g/kg

Stabiliser:

Stabiliser may be present in the technical material at a maximum level of 100 g/kg.

Impurities:

O,O,O',O'-tetraethyl dithiopyrophosphate (S,S-TEPP, sulfotepp): 2.5 g/kg maximum
O,O,O',O'-tetraethyl-monothiopyrophosphate (O,S-TEPP, monotepp): 0.2 g/kg maximum

All approved sources of diazinon meet the NRA's Minimum Compositional Standard and FAO Specifications, for diazinon.

2.8 FAO Specifications for Diazinon Emulsifiable Concentrates

Active: The diazinon content shall not differ from the label content by more than the following amounts:

Declared content	Permitted tolerance
Up to 500 g/L or g/kg	± 5% of the declared content
Above 500 g/L or g/kg	± 25 g

Impurities:

S,S-TEPP: Maximum = 2.8x A mg/kg, where A is the label content in g/kg. For example, a diazinon product containing 100 g/kg, the maximum permitted S,S-TEPP content would be 2.8 x 100 = 280 mg/kg
O,S-TEPP: Maximum = 0.22 x A mg/kg, where A is the label content in g/kg. For example, a diazinon product containing 100 g/kg, the maximum permitted O,S-TEPP content would be 0.22 x 100 = 22 mg/kg
Water: Maximum = 2 g/kg

2.9 FAO Specifications for Diazinon Hydrocarbon-Based Solutions

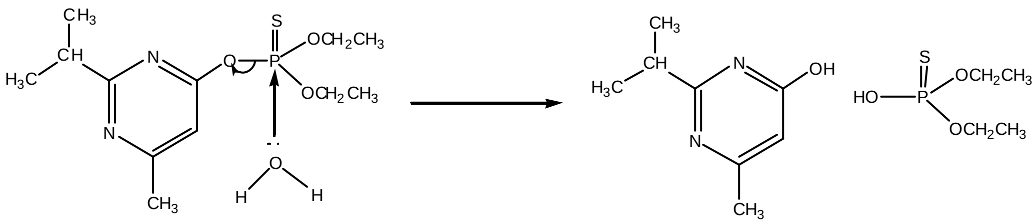
Active: The diazinon content shall not differ from the label content by more than the following amounts:

Declared content	Permitted tolerance
Up to 200 g/L or g/kg	± 10% of the declared content
Above 200 g/L or g/kg	± 20 g

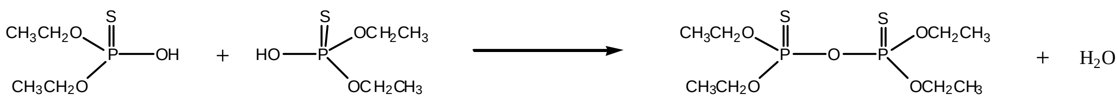
Impurities:
S,S-TEPP: Maximum = 2.8x A mg/kg, where A is the label content in g/kg. For example, a diazinon product containing 100 g/kg, the maximum permitted S,S-TEPP content would be 2.8 x 100 = 280 mg/kg
O,S-TEPP: Maximum = 0.22 x A mg/kg, where A is the label content in g/kg. For example, a diazinon product containing 100 g/kg, the maximum permitted O,S-TEPP content would be 0.22 x 100 = 22 mg/kg
Water: Maximum = 2 g/kg

2.10 Formation of Toxic Impurities

In excess water, the principal products of hydrolysis of diazinon are diethylthiophosphoric acid and 2-isopropyl-4-methyl-6-hydroxypyrimidine. Under the reaction conditions, diethylthiophosphoric acid is further hydrolysed to ethylthiophosphoric acid, thiophosphoric acid and ultimately phosphoric acid, which is non-toxic.

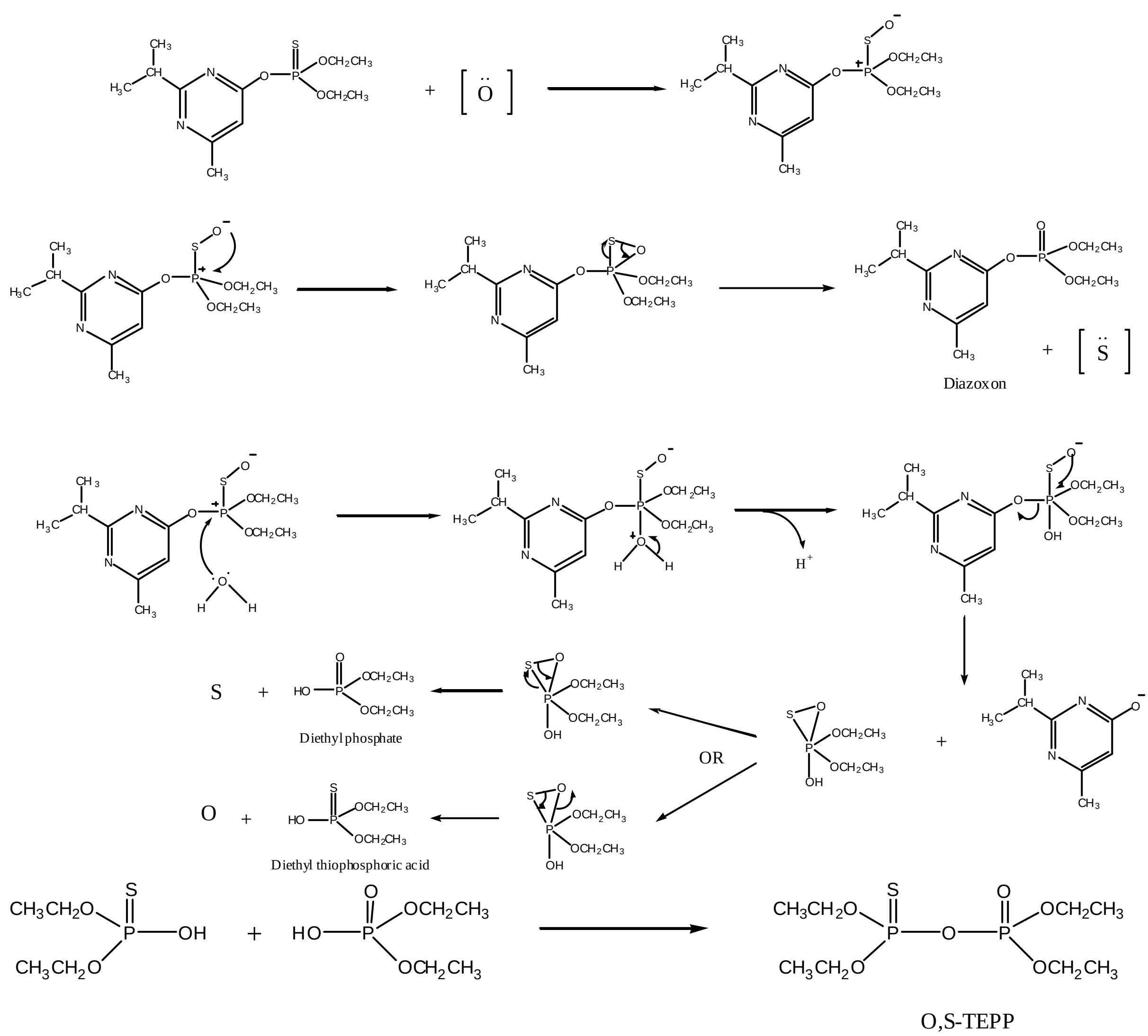


On the other hand, the presence of only **trace amounts** of water leads to the formation of the toxic impurities S,S-TEPP and, O,S-TEPP. The initial hydrolysis of diazinon gives diethylthiophosphoric acid and 2-isopropyl-4-methyl-6-hydroxypyrimidine (see above). Two molecules of diethylthiophosphoric acid can combine in an acid catalyzed or radical initiated dimerization (radical ions are formed by UV radiation) to form the S,S-TEPP.

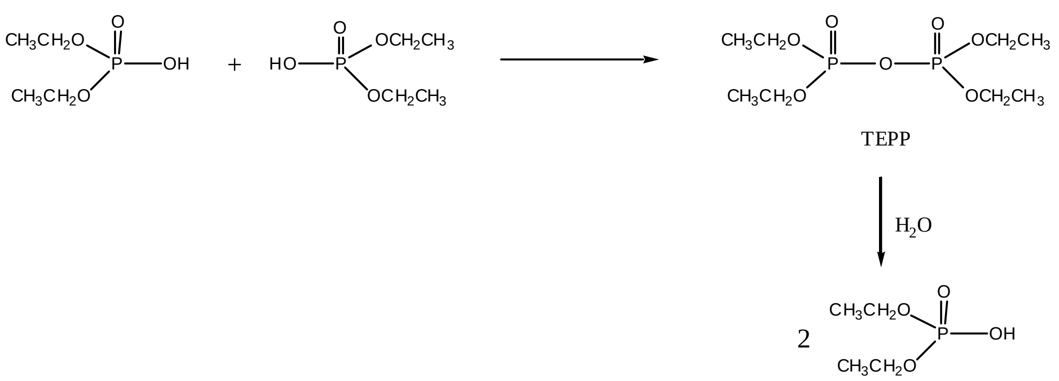


S,S-TEPP

The formation of O,S-TEPP occurs in a similar manner: the diazinon undergoes oxidation and hydrolysis to diethylphosphoric acid, which subsequently combines with diethylthiophosphoric acid to form the O,S-TEPP. The proposed mechanism of oxidation followed by hydrolysis is outlined below:



Similarly, simultaneous oxidation and hydrolysis of diazinon in the presence of a small amount of water lead to the formation of TEPP, which is formed by the combination of two molecules of diethylphosphoric acid. However, TEPP is rapidly hydrolysed by water even at room temperature [DT_{50} (50% decomposition) of TEPP and S,S-TEPP is 6.8 hours and 8.2 days respectively, in neutral aqueous solution at 25^0C] forming diethylphosphoric acid, which is non-toxic to both insects and animals. TEPP is therefore not present in decomposed samples (O,S-TEPP and S,S-TEPP are more stable).



The TEPP compounds are stabilised with respect to hydrolysis by the increasing number of thiono groups, therefore, the order of hydrolysis is TEPP > O,S-TEPP > S,S-TEPP. The finding of S,S-TEPP, smaller quantities of O,S-TEPP and no TEPP in the decomposed samples are in accordance with their hydrolytic stabilities.

2.11 Stability and Effect of Aging on Acute Toxicity

A number of diazinon-related deaths have been reported in companion animals and cattle. The main concern with diazinon products is the formation of breakdown products, particularly S,S-TEPP and O,S-TEPP. These degradation products (O,S-TEPP and S,S-TEPP) are much more toxic than diazinon and are formed from diazinon in the presence of a small amount of moisture, air, heat (elevated temperatures) and ultraviolet radiation. Therefore, the exclusion of water in diazinon source material as well as in the hydrocarbon-based/emulsifiable concentrate (EC) formulated products is absolutely necessary to guarantee the stability of diazinon and its formulations. Corroded metal containers and metal ions also contribute to the catalytic decomposition of diazinon to the toxic degradation products.

Substances that react with water/acids are commonly used as stabilisers in diazinon source material and formulated products based on hydrocarbon solvents/EC. Epoxides, such as epoxidised soybean oil, are used as stabilisers. Epoxide stabilisers react with water and acids, thereby reducing the risk of these contaminants reacting with diazinon. The presence of sufficient stabiliser (acid, water scavenger) prevents the initial hydrolysis of diazinon and subsequent reaction to form toxic degradation products. It should be noted that the stabiliser loses its activity when all of the epoxy groups have reacted. The duration of the stabiliser activity depends on factors such as storage temperature, stabiliser content and water content.

The presence of adequate epoxidized soybean oil has significantly reduced the risk of formation of toxic breakdown products in diazinon source material and hydrocarbon-based/EC formulated products. The stabiliser is normally added at two stages, immediately after synthesis of the source material, then again at the stage of formulation of hydrocarbon-based/EC product. The level of stabiliser in hydrocarbon-based/EC formulated product often depends on the proposed use pattern.

As a result of the improvements in manufacturing process and inclusion of appropriate stabilisers, the acute oral LD_{50} of diazinon source material has increased from 250 mg/kg to 1250 mg/kg in the rat.

In 1993, the NRA co-ordinated a survey in which a total of 159 unopened, off-the-shelf liquid diazinon products ranging from dog washes to sheep dips (available from retail outlets throughout Australia), were tested for diazinon content and the presence of S,S-TEPP and O,S-TEPP. It was found that 13 of these samples (8.2% of total) contained S,S-TEPP at levels above the FAO benchmark impurity limits for S,S-TEPP and 7 samples (4.5% of total) exceeded the FAO benchmark impurity limits for O,S-TEPP. In addition 35 samples (22% of total) failed to meet the product specifications ($\pm$ 10% label claim) for the active constituent (diazinon).

2.12 Product Stability

The stability of non-aqueous liquid diazinon products has been a concern to the chemical industry and the APVMA. This concern arises from the formation of toxic degradation products on storage. These toxic compounds are formed when diazinon products react with small amounts of water, as discussed above. These degradation products are believed to be the cause of death of a number of companion animals, as well as cattle, and to contribute to the occupational health risk to workers exposed to these products.

2.13 Assessment outcomes related to product cancellations and conclusion

The formation of toxic degradation products following unsuitable storage conditions of specific diazinon products is considered to be the likely reason for reported cases of fatal companion animal, cattle intoxications and occupational hazards attributed to diazinon. The risk associated with this potential problem can be substantively reduced if not eliminated by the inclusion of the stabilising agent, epoxidised soybean oil, into the diazinon source material and hydrocarbon-based/EC formulated product, thereby reducing the risk of formation of toxic degradation products during storage. All hydrocarbon-based/EC formulations of diazinon should include sufficient stabiliser, and be packed and stored under conditions that are not conducive to the formation of acutely toxic products.

In excess water, diazinon is hydrolyzed to give non-toxic by-products. Thus, water-based formulations containing diazinon do not represent a risk in the same way as source material and hydrocarbon-based/EC formulations. In the presence of a small quantity of water, in the order of 0.2 to 2.0%, diazinon decomposes to give the highly toxic degradation products S,S-TEPP and O,S-TEPP (these degradation products are 300- and 2500-fold respectively more toxic than diazinon). Consequently, source material and hydrocarbon-based/EC formulations must contain adequate levels of stabiliser. Solid formulations of diazinon, using carriers of faintly alkaline character, are able to postpone or inhibit the deterioration.

With reference to hydrocarbon-based/EC formulations it is concluded that:

- Highly toxic degradation products (S,S-TEPP and O,S-TEPP) are formed when non-aqueous liquid formulations of diazinon are stored under unsuitable conditions;
- Trace amounts of water lead to decomposition, therefore, it is important to exclude the water by addition of additives that absorb water and hence prevent hydrolysis of diazinon;
- The stability of hydrocarbon-based/EC formulations of diazinon depends on several factors including composition of the formulation, water content of the formulation (traces of moisture may be present in solvents and other excipients used), storage conditions (temperature, moisture uptake, container type, UV light etc), and amount of stabiliser added.

Products containing diazinon that are based on hydrocarbon solvents formulated without adequate stabiliser are considered to be a risk to public health and animal safety.

2.14 References

Diazinon, International Programme on Chemical Safety, WHO, Environmental Health Criteria 198, p.4.

NRA Guidelines for the Generation of Storage Stability Data of Agricultural Chemical Products, February 2002.
http://www.nra.gov.au/guidelines/stability_guidelines.pdf.

3. ENVIRONMENTAL ASSESSMENT

3.1 Introduction

This is an extract of the assessment presented in the draft report for the reconsideration of diazinon. It only includes information that is relevant to the recommendations related to product cancellation on environmental grounds. For additional information regarding the findings of the APVMA related to other parts of the reconsideration, please refer to the relevant component of the final report. Pending completion of any component please refer to the draft report titled '*The NRA draft review of diazinon, Volumes I & II, August 2002*'.

3.2 Environmental fate and degradation

3.2.1 Hydrolysis

From three experiments, it was concluded that hydrolysis of diazinon is relatively slow at pH 7 and 9 and diazinon is classified as slightly hydrolysing. At pH 5 the hydrolysis is faster and diazinon is classified as fast to moderately hydrolysing. There was one major metabolite, 6-hydroxy-2-isopropyl-4-methylpyrimidine (the principal metabolite). Hydrolysis could be a significant contributor to the overall degradation of diazinon in the environment under acidic conditions.

3.2.2 Photolysis

Aquatic

In 3 laboratory studies using artificial lamps there was significant photodegradation in water. The half-lives were determined for two studies only and ranged from 55.9 to 122 hours but the half-life under environmental conditions was not determined. There was only one metabolite identified, the principal metabolite above.

Two studies showed that degradation in natural sunlight occurred but only one study determined a half-life of 49 days. A study performed to German guidelines showed that direct aquatic photodegradation of diazinon is unlikely under environmental conditions.

It was concluded that photodegradation in water is unlikely to be a significant route of in the environment.

Soil

Based on 3 soil photolysis studies using natural sunlight, the half-life of photodegradation of diazinon in dried soils was calculated to between 17.5-37.4 hours. The major metabolite was the principal metabolite, as above.

There were 3 additional studies that used artificial light, with half-lives of 55 hours and 5.5 days determined in two. A half-life was not determined in the other study. These studies cannot be readily related to natural conditions.

Photodegradation on soil could be a route of environmental degradation in Australia, given the high light levels during summer.

3.2.3 Metabolism

Only one metabolism aerobic metabolism study was performed to current guidelines.

Aerobic Soil Metabolism

The degradation of diazinon under aerobic conditions in soil is rated as fast to moderate. In the most reliable study the half-life ranged 4.5 to 8 days under a range of conditions and was between 11 to 59 days in other studies. The initial product was the principal metabolite from hydrolysis, which was then slowly degraded and mineralised.

The mineralisation of diazinon technical was compared to a formulated product (microencapsulated, CS) under aerobic conditions. The study showed little difference on the rate of mineralisation but the rate of degradation in the CS formulation was significantly slower than for the TGAC, with 26.1% versus 1.0% of active remaining after 12 weeks.

In a review of literature studies on the degradation of diazinon in soil, the time for 50% degradation is stated to be between 2 and 5 weeks. This is dependent on temperature, moisture and pH as expected.

Aerobic Aquatic Metabolism

The degradation of diazinon in aerobic aqueous conditions is relatively fast, with a half-life of between 7-15 days in natural river and pond water/soil systems. The degradation pathway appears to be hydrolysis followed by mineralisation of the hydrolysis product.

In an older study, the concentration of diazinon in water and pond sediment decreased 93% after 9 days. In a literature study, the degradation of diazinon was studied using both non-sterile and sterile soil/water systems. The results show that diazinon disappeared with half-lives between 8.8-17.4 days for non-sterile systems and 33.8-43.8 days in the sterile systems.

Anaerobic Aquatic Metabolism

No studies were presented.

3.2.4 Mobility

Soil adsorption/desorption

The soil adsorption/desorption of diazinon was determined in six soils and showed that diazinon is moderately absorbed. The adsorption was strongly dependent on the organic content of the soil. In a literature report on the adsorption of diazinon in 25 different soils, the adsorption was moderate to strong. Diazinon can be rated as having medium mobility in soil.

Leaching

In 2 soil column leaching studies using eight different soils, there was no leaching of diazinon but the metabolites were detected in the leachate. Using aged soil, it was shown that the metabolites from soil degradation are more mobile than diazinon itself. It is concluded that leaching of diazinon is unlikely but that the metabolites could leach.

Volatility

A study on the volatilisation of diazinon from soil concluded that volatility from soil is low but the study was not conducted to current guidelines. The volatility from plant and soils, studied according to German guidelines, showed 9% loss of diazinon with most of this loss assumed to be diazinon from the plant surfaces.

Volatilisation of diazinon from soils is not expected to be a significant route for the dissipation from soil but volatilisation from other non-adsorbing surfaces and plant foliage could be possible. According to literature reports diazinon is the most commonly detected organophosphate detected in air, rain and fog in the US.

3.2.5 Field Dissipation Studies

Bare Soil

Ten bare soil studies were presented, performed according to either German or US EPA guidelines. The German soils were classified as silt loams and the US soils as loamy sands or sandy soils. The results of all these studies clearly showed that even under conditions conducive to leaching, the movement of diazinon was minimal. The major metabolite did show some leaching behaviour but significant contamination of ground water would not be expected. The half-life of diazinon ranged from 4-16 days, with one at 27 days, and that for the principal metabolite was between 7-24 days.

Field Crops

Six field crop studies were performed according to US EPA guidelines. The study sites were largely the same as those used for the bare soil studies. These studies were performed as for the bare soil studies, except that multiple applications were made. The first half-life of diazinon was between 2.8 to 13 days and between 8 to 24 days for the principal metabolite.

Lysimeter Study

A three year lysimeter study was performed according to German guidelines to investigate the leaching behaviour of diazinon. Crops were grown in the lysimeters which were treated as per normal agricultural practice. The results confirmed previous results that diazinon did not leach, though the principal metabolite did leach but at low concentrations.

Runoff monitoring studies

Three agricultural runoff and pond monitoring studies were performed as special studies in three different apple orchards in Pennsylvania, USA. The orchards were treated 6 times with diazinon under normal commercial practice. At each site there was a pond beside the orchards that received runoff.

The field runoff data from the 3 orchard sites showed that runoff from treated areas could cause relatively high concentrations in ponds, with the highest levels in the ponds occurring immediately after application. While spray drift was a significant contributor to residues in the pond, this route of exposure did not appear to account for all the residues found. The maximum concentration in ponds due to runoff only was 5.6 µg/L, which occurred 14 days after the last application following heavy rain. The half-lives determined in these ponds under environmental conditions mainly in summer in the USA ranged from 2.2 days to 19.7 days and correspond closely with that in the aquatic metabolism study of 7 to 15 days. Levels in sediment were low.

3.2.6 Environmental exposure

In Australia diazinon has been detected in surface water drains from farms twice during 1991-1993 and once in 1994-1995 at 0.13 µg/L. In the US EPA preliminary risk assessment report, published on their web site, water monitoring studies showed that diazinon is a wide spread contaminant in surface waters, especially in urban areas. Diazinon is reported in major USA rivers, including the Rio Grande, Mississippi and the Columbia. The finding of diazinon in these very large rivers is extremely significant given the size of the river flow, indicating the total mass of the pesticide in these rivers is high.

3.2.7 Bioaccumulation

The steady state bioaccumulation factors were determined to be low from a fish bioaccumulation study, with the highest being 540X for non-edible tissues. Elimination of diazinon from these tissues was rapid, with a half-life of between 1 and 3 days, indicative of rapid depuration. Bioaccumulation in the aquatic environment is not expected.

A bio-concentration study using aged soil metabolites was performed according to older US EPA guidelines. The study showed that there is unlikely to be bioaccumulation of diazinon or its metabolites.

3.2.8 Conclusion

Diazinon is readily degradable aquatic environments and moderately to readily degradable in soils. Bioaccumulation is not expected. Due to the moderate binding in soil and rapid degradation, leaching is not expected. However, as the principal metabolite is more stable and mobile in soils, it could leach in soils that are prone to leaching.

While diazinon is not volatile from soil, it is slightly volatile from leaves and other surfaces. No information was presented on the photolysis in the vapour phase, but based on the ready degradation of other organophosphates in the atmosphere diazinon vapours are not expected to persist in the air.

3.3 Ecotoxicity in relation to product cancellations

Diazinon is toxic to most organisms and in particular aquatic invertebrates.

3.3.1 Aquatic organisms

The toxicity to aquatic organisms, especially invertebrates, is very high. The acute toxicity to fish from submitted studies (9 species) ranges from LD50 of 2.16 mg/L for common carp to 23.4 mg/L for crucian carp. Life cycle studies have not been performed but the embryonic and larval life stages of fathead minnow, normally considered the most sensitive, have been tested and the MATC was determined to be between 0.092 and 0.17 mg/L. In a database of regulatory-type studies that have been reviewed by US EPA, the toxicity to fish ranges from LC50 of 0.09 mg/L for rainbow trout to LC50 of 7.8 mg/L for fathead minnow.

Diazinon is extremely toxic to invertebrates, which is typical for an organophosphate, with acute toxicity figures for C*eriodaphnia* (EC50) of between 0.36-0.6 µg/L and for mysid shrimp EC50 = 4.2 µg/L. The chronic toxicity to daphnia has been determined and the MATC found to be between 0.17 and 0.32 µg/L. The US EPA database on reviewed regulatory studies gives the most sensitive species as scud, EC50 = 0.2 µg/L, and least sensitive invertebrate as grass shrimp EC50 = 28 µg/L. The acute EC50 for *Daphnia magna* (three studies) in this database ranged from 0.96 to 1.1 µg/L.

Diazinon is moderately toxic to green algae, with EC50s of 8.5 and 6.4 mg/L for two species.

3.3.2 Mesocosms

In a detailed long term study, diazinon was applied to several mesocosms at several treatment rates. The maximum average concentrations of diazinon, which mainly occurred immediately after the sixth (last) application, ranged from 2.3 to 29.7 µg/L.

It should be noted that in treatment levels 4 and 5, one pond (replicate) showed consistently lower concentrations and more rapid degradation than the other two ponds. The half-life of diazinon decreased with increasing number of applications, and ranged from 10-26 after the first application to 5.5 to 8.5 days after the sixth application.

There were no detrimental effects on fish or plants at any treatment except for diatoms and green algae. Diatoms were significantly affected at the highest treatment with occasional reductions at lower levels and green algae affected occasionally, which is surprising given the acute toxicity results above.

Invertebrates were significantly affected by diazinon. For zooplanton, Cladocerans were the most sensitive taxon, significantly reduced at all levels, followed by rotifers and Copepods. For higher macroinvertebrates, Trichoptera were the most sensitive order reduced at all treatments, with Diptera and Ephemeroptera intermediate and gastropods essentially unaffected. All organisms recovered by the end of the study period, with Cladocerans taking the longest, up to 4 months.

It is concluded that while diazinon can significantly affect aquatic organisms at relatively low concentrations, especially invertebrates, these affected organisms are likely to recover and there is unlikely to be significant long term effects on populations, provided organisms are given adequate time to recover.

3.3.4 Non-Target Invertebrates

Diazinon is extremely toxic to bees by all routes of exposure. There were no regulatory studies presented but an old literature report gives LD50s of 0.22 µg/bee (contact) and 0.20 µg/bee (oral). In addition, more recent literature reports show that the toxicity to bee larvae is extremely high, with an LD50 of 0.000121 µg/bee. The US EPA database shows contact toxicity as 0.2 µg/bee and foliage contact LC50 as 0.28 kg/ha.

In studies conducted by the IOBC, it was shown that diazinon is harmful to parasitic wasps, predatory mites and spiders tested in laboratory exposed conditions and less harmful in the laboratory "protected" tests. The semi-field tests showed that fresh residues of diazinon were harmful to the test organisms and the toxicity was rated as slightly persistent to persistent (5 days to >30 days). The field tests showed that diazinon was harmful (more than 99% mortality) to the predatory mite tested.

Several of the genera of the species tested are found in Australia and are used as part of IPM programs. Most of the mite genera tested are also present in Australia and are used in IPM programs, together with predatory beetles.

It is clear that diazinon is likely to significantly affect important beneficial insects in Australia.

The toxicity of diazinon to earthworms was tested according to OECD Guidelines with a LD50 130 (CI 110-160) mg/kg of soil. The toxicity of diazinon to earthworms has been tested under semi-field conditions and there was a maximum of 20%

mortalities at the highest level, 20 kg/ha. The results indicate that there is unlikely to be significant mortalities of earthworms at less than 20 kg/ha.

Diazinon has limited effects on micro-organisms. In tests using two different soil types, there was minimal effect on soil respiration and nitrification at 16 and 80 mg/kg soil, corresponding to 12 and 60 kg ai/ha. Literature reports give the EC50 as 10.3 mg/L to a bacteria using the Microtox system. There were only limited effects on respiration of sewage micro-organisms at 100 mg/L.

3.4 Predicted environmental hazard in relation to product cancellations

3.4.1 Chronic Effects

Once in the aquatic environment, diazinon is expected degrade. The range for the laboratory half-lives in natural water was 7-17 days (average 11 days) for the initial period of degradation. In the mesocosm study, the half-lives ranged from 5.4 days to 8.6 days during the period with warmer water (26 °C) but were up to 18 days in colder water.

In the mesocosm study, the sensitive cladocerans did not recover for some 9 weeks after the last application but the time taken was in part due to the time for recruitment to occur.

3.5 Assessment outcomes in relation to product cancellations and conclusions

The disposal of dog washes could be a significant source for the diazinon that is released in Sydney sewage treatment plant effluent. The levels of diazinon that have been detected in sewage effluent by Sydney Water could significantly affect a range of aquatic invertebrates and are considered unacceptable as they are up to >100 times the ANZECC water quality guideline of 0.01 µg/L. At many times during the year the river flow is insufficient to adequately dilute levels below this guideline. Other sewage treatment plants throughout Australia may be similarly affected.

The label statement “Do not dispose of used wash solutions or unused product down storm water drains or sewers” was proposed. However, the lack of an alternative option has been identified, with disposal to garden soil or lawns not supported on health grounds, and is impractical when dogs are washed in laundry tubs etc. As a result it is recommended that these products be removed from the market.

Particular concerns arise in urban areas. Use of companion animal products appears to give rise to excessive concentrations in sewage effluent in the Sydney region and probably in other cities. As this cannot be dealt with by the inclusion of appropriate label statements, it is concluded that continued use of products containing diazinon that are dog and kennel flea treatments may have a harmful effect on the environment.

4. REGULATORY APPROACH FOR THE RECONSIDERATION OF SELECTED DIAZINON PRODUCTS

4.1 Regulatory options

The basis for a reconsideration of the registration and approvals for a chemical is whether the APVMA is satisfied that the requirements prescribed by the Agvet Codes for continued registration and approval are being met. These requirements are that the use of the product, in accordance with the recommendations for its use:

- would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues;
- would not be likely to have an effect that is harmful to human beings;
- would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment;
- would not unduly prejudice trade or commerce between Australia and places outside Australia; and
- would be effective for the purposes claimed.

The requirements for product labels are that the label contains adequate instructions. Such instructions include:

- the circumstances in which the product should be used;
- how the product should be used;
- the times when the product should be used;
- the frequency of the use of the product;
- the withholding period after the use of the product;
- the disposal of the product and its container;
- the safe handling of the product.

There are three possible outcomes to the reconsideration of the registration of products containing diazinon and their labels. Based on the information reviewed the APVMA may be:

- satisfied that the products and their labels continue to meet the prescribed requirements for registration and approval and therefore confirms the registrations and approvals.
- satisfied that the conditions to which the registration or approval is currently subject can be varied in such a way that the requirements for continued registration and approval will be complied with and therefore varies the conditions of registration or approval.
- not satisfied that the requirements for continued registration and approval continue to be met and suspends or cancels the registration and/or approval.

4.2 Assessment outcomes

The major concern regarding continued registration of products that are unstabilised hydrocarbon formulations is that highly toxic degradation products may form when they are stored under unsuitable conditions. Trace amounts of water can lead to decomposition to sulfotepp and monotepp. Compared to the parent diazinon, sulfotepp and monotepp are 300-fold and 2500-fold more toxic, respectively.

The products are registered for use as sheep dips and wound dressings to control blowfly strike and protect against lice, for use as commercial building treatments and for use in the home garden as ant sprays, lawn insect killers and insecticides for use on vegetables and fruit.

These products are therefore considered to be a risk to public health and animal safety because the presence of a small amount of water in the formulation can result in breakdown to toxic substances. To mitigate the risk the products would require reformulation. However reformulation may have implications for other aspects of safety and efficacy of the product.

The environmental assessment found that diazinon is acutely toxic to aquatic organisms at relatively low levels. Several products that contain diazinon are registered for use on dogs and in yards and kennels for the control of ticks, fleas and lice.

The assessment concluded that wastewater and runoff from dog and kennel treatments could be a significant source for the diazinon that is released in Sydney sewage treatment plant effluent. Diazinon has been detected in sewage effluent at levels >100 times ANZECC water quality guideline of 0.01 µg/L. The levels detected are likely to have a significant effect on a range of aquatic invertebrates. Other sewage treatment plants throughout Australia may be similarly affected.

Products containing diazinon that are dog and kennel flea treatments are therefore considered to be a risk to the environment.

4.3 Proposed Regulatory Approach

The APVMA will address the potential risks identified in this report using the following regulatory actions.

The APVMA will cancel registration of products containing diazinon that are hydrocarbon-based formulations, including emulsifiable concentrates, but do not contain adequate stabiliser, and all associated label approvals on toxicological and animal safety grounds. The APVMA cannot be satisfied that continued registration would not be a risk to public health and animal safety. The APVMA is not satisfied that the conditions of registration of these products can be varied in such a way that the requirements for continued registration will be complied with.

The APVMA will cancel registration of products containing diazinon formulated as stabilised emulsifiable concentrates for use on companion animals and associated label approvals on environmental grounds. The APVMA cannot be satisfied that continued registration would not have a harmful effect on the environment. The APVMA is not satisfied that the conditions of registration of these products can be varied in such a way that the requirements for continued registration will be complied with.

Product registrations and associated label approvals to be cancelled are listed in Table 3.

Table 3 Product and label cancellations

Product number	Product name	Registrant	Label approval number(s)
31960	Hortico Ant Killer Spray Insecticide	Hortico (Aust) Pty Ltd	Ψ 31960/0700
40019	Gammawash D Insecticidal Dog Wash	Wesfarmers Landmark Limited	Ψ
40653	Exelpet Yard and Kennel Flea Control Concentrate	Exelpet Products (a division of Effem Foods Pty Ltd)	Ψ 40653/1197
41307	Hortico Lawn Grub & Insect Killer	Hortico (Aust) Pty Ltd	Ψ 41307/0800
41783	Diazol Sheep Dip, Jetting Fluid and Blowfly Dressing	Makhteshim-Agan (Aust) Pty Ltd	Ψ
49853	Nucidol 200 Dog Wash	Novartis Animal Health Australiasia Pty Ltd	49853/01 49853/0498

Ψ Label transitioned from the States and so not having an approval number.