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DRAFT

The NRA Review of

DIAZINON

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- suggest to the NRA any alternative solution you may have for the issue.

Please try to structure your comments in point form referring each point to the relevant section in the Review Summary or the technical report. This will help the NRA assemble and analyse all of the comments it receives.

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ABBREVIATIONS AND ACRONYMS

μg	microgram
ACPH	Advisory Committee on Pesticides and Health
ADI	acceptable daily intake (for humans)
ACGIH	American Conference of Governmental Industrial Hygienists
ARfD	Acute Reference Dose
ai	active ingredient
BEI	Biological exposure index
ChE	cholinesterase
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
EEC	estimated environmental concentration
GAP	Good Agricultural Practice
GLP	Good Laboratory Practice
h	hour
ha	hectare
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
IPM	integrated pest management
IV	Intravenous
kg	kilogram
L	Litre
LC$_{50}$	concentration that kills 50% of the test population of organisms

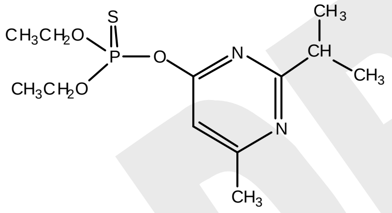
LD$_{50}$	dosage of chemical that kills 50% of the test population of organisms
LOEL	lowest observed effect level
ME	microencapsulated
mg	milligram
mg/kg bw/day	Mg/kg bodyweight/day
MOE	margin of exposure
MRL	maximum residue limit
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NOEL	no observed effect level
NOHSC	National Occupational Health and Safety Commission
OP	organophosphate pesticide
POEM	Predicted Operator Exposure Model
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
RBC	red blood cells/erythrocyte
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TCP	trichloro pyridinol
ULV	ultra low volume
USEPA	United States Environment Protection Agency
WHP	withholding period

1. 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.

1.1 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.**

1.2 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 x 10^{-4} mmHg at 25 ^{o}C
Refractive index ($_{n}D^{20}$)	1.4978-1.4981 (20 ^{o}C)
Volatility (at 20 ^{o}C)	2.3 mg/m^3

pH at 20 ^{o}C	Approximately 6.0
Solubility in water	40 mg/L at 20 ^{o}C (Novartis); 60 mg/L at 20 ^{o}C (WHO, 1998)
Solvent solubility (at 20 ^{o}C)	Completely miscible in acetone, methanol, ethanol, chloroform, acetonitrile, cyclohexane, dichloromethane, hexane, benzene, petroleum ether, and carbon disulfide
Specific gravity at 20 ^{o}C	1.116-1.118
Viscosity at 20 ^{o}C	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

1.3 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 ^{o}C)	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 x 10^{-4} mmHg at 20 ^{o}C
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 ^{o}C)	13 to 14 mPa.s (Novartis)
Hydrolysis (at 20 ^{o}C)	pH 3.1, $t_{½}$ = 11.8 hours
Flammability	The flashpoint is over 170 ^{o}C by open cup
Ignition temperature	360 ^{o}C
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

1.4 Scheduling

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

1.5 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.

1.6 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.

1.7 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.

1.8 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

1.9 FAO Specifications for Diazinon Hydrocarbon-Based Solutions

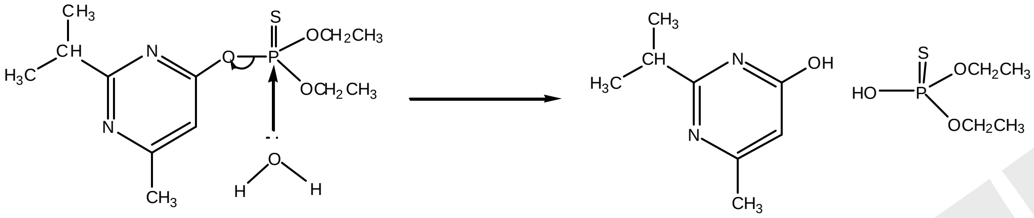
Active: The diazinon content shall not differ from the label content by more than the following amounts:

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

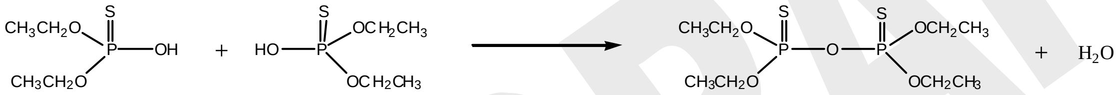
Impurities:
S,S-TEPP: Maximum = 2.8x A mg/kg, where A is the label content in g/kg. For example, a diazinon product containing 100 g/kg, the maximum permitted S,S-TEPP content would be 2.8 x 100 = 280 mg/kg
O,S-TEPP: Maximum = 0.22 x A mg/kg, where A is the label content in g/kg. For example, a diazinon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

1.10 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. This information is supported by available stability data.

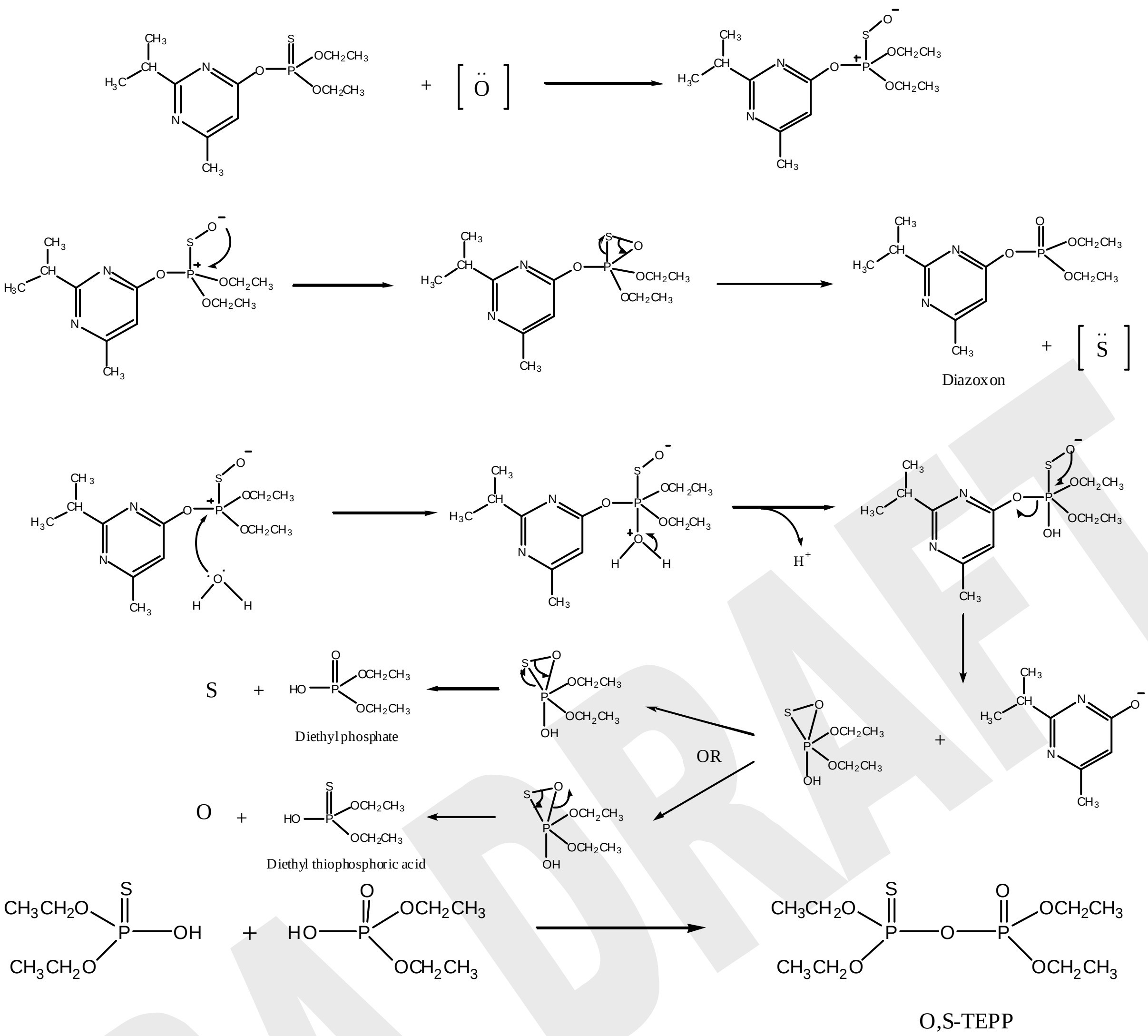


On the other hand, the presence of only **trace amounts** of water leads to the formation of the toxic impurities S,S-TEPP and, O,S-TEPP. The initial hydrolysis of diazinon gives diethylthiophosphoric acid and 2-isopropyl-4-methyl-6-hydroxypyrimidine (see above). Two molecules of diethylthiophosphoric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

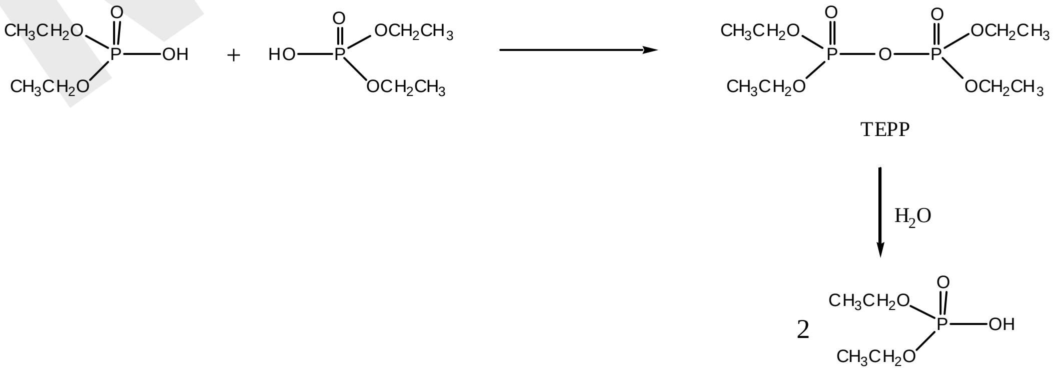


S,S-TEPP

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 $25^{0}C$] 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.

1.11 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 (see toxicology section of the review), 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[1].

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 (± 10% label claim) for the active constituent (diazinon).

1.12 Real-Time Stability Data

The stability of non-aqueous liquid diazinon containing products has been a concern to the chemical industry and the NRA. 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.

Products containing diazinon are date-controlled products. Such products are required to include a shelf life on the label.

A real time stability data study on one stabilised liquid hydrocarbon/EC formulated diazinon product under actual in-use conditions has now been presented to the NRA in support of a shelf life of 36 months. On this basis it is recommended that the NRA affirm a shelf life of up to 12 months for any other stabilized liquid hydrocarbon/EC formulated products unless stability data to support a longer shelf life has been provided to the NRA. Any stability study in support of an extended shelf life should be conducted in accordance with the NRA's guidelines for such studies[2].

Amendment to the shelf life is not recommended for other formulations of diazinon (including dusts and powders, water based microencapsulated and solid formulations).

1.13 Recommendations

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, refer to toxicology report). 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.

Therefore the following regulatory actions are recommended on chemistry grounds:

With reference to the active diazinon it is recommended that:

(1) The NRA affirm all approved sources of the active diazinon.

With reference to solid formulations such as dusts, flea collars, insecticidal powders and cattle ear tags, and aqueous liquid formulations (microencapsulated aqueous concentrates and emulsions in water), it is concluded that:

- Diazinon will break down without formation of significant amounts of highly toxic degradation products;
- It is accepted that these formulations are less likely to present a stability problem; and
- The current shelf life for such products will apply.

It is therefore recommended that

(1) The NRA affirm registration of these types of products.

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.

It is therefore recommended that

(1) Hydrocarbon-based/EC diazinon products that do not contain stabiliser should be cancelled.
(2) Hydrocarbon-based/EC diazinon products that contain stabilizer should be packaged in glass or metal containers pre-coated with inert material inside (epoxy-lined) and stored under conditions that are not conducive to the formation of acutely toxic impurities. [Note: moisture permeable containers (eg low density polyethylene) increase the risks highlighted above, and should not be used for storing hydrocarbon-based/EC diazinon products.]
(3) The NRA should affirm a shelf life of no more than 12 months for products of this type unless supported by stability data for a longer shelf life.

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

- Application of hydrocarbon-based/EC diazinon products past the recommended expiry date presents a risk.

It is therefore recommended that

(1) label instructions for hydrocarbon-based/EC diazinon product should include the following statements:
“**The toxicity of this diazinon product may increase markedly over time. DO NOT use this product if it is out-of-date**”;
“**Store in tightly closed original containers under cool, dry, dark conditions**”. This statement should appear under the heading ‘Storage and Disposal’, and
“**Do not allow water to enter this container. Do not rinse the lid with water**”.

Although stabilized EC formulations currently may be diluted in kerosene or oil in addition to water, there is a theoretical risk associated with the preparation of stabilised EC formulations in hydrophobic solutions like kerosene or oil.

It is therefore recommended that

1. label instructions for hydrocarbon-based/EC diazinon product that currently allow the dilution of these products in hydrophobic solutions like oil or kerosene should be deleted.
2. label instructions should include the following statement:
“**Do not use oil or kerosene to dilute this product. Dilute this product in water only.**”

With reference to labels for other diazinon products, additional label statements are not recommended.

1.14 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.