Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active Decoquinate in the product Deccox

APVMA Product Number 54134

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Director Public Affairs
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604
Australia

Email: communications@apvma.gov.au

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CONTENTS

PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing, Office of Chemical Safety (OCS), Department of the Environment (DotE), and State Departments of Primary Industries.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents.

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined in the APVMA's regulatory guidelines.

This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target animal safety.

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding

whether to grant the application. These matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **24 February 2016** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All information judged by the APVMA to be ***confidential commercial information (CCI)***[1] contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the **grounds for registration** should be addressed in writing to:

Enquiries
Registration Management and Evaluation
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: (02) 6210 4701
Fax: (02) 6210 4721
Email: enquiries@apvma.gov.au

[1] A full definition of 'confidential commercial information' is contained in the Agvet Code.

Further information

Further information can be obtained via the contact details provided above.

Further information on public release summaries can be found on the APVMA website: www.apvma.gov.au.

1 INTRODUCTION

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Zoetis Australia Pty Ltd for registration of a new product, **DECCOX**, containing the new active constituent. decoquinate.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of **DECCOX**, and approval of the new active constituent.

Decoquinate is a chemically synthesized 4-hydroxyquinolone anti-protozoan agent. **DECCOX** is a feed additive and an oral powder that contains 60 g/kg decoquinate. The proposed use is for the prevention and control of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. mivati*, *E. maxima* and *E. brunetti* in broiler chickens.

DECCOX is administered in complete feed at an inclusion of 500 g of **DECCOX** in each tonne of feed to provide 30 mg decoquinate per kilogram. The medicated feed is fed to broiler chickens as the only source of feed from day old to slaughter.

DECCOX will be packaged in 25 kg containers.

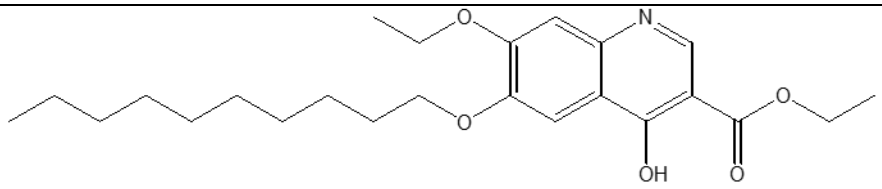
DECCOX is registered in the EU, USA, Japan, New Zealand, China, Taiwan and Korea.

The APVMA seeks public comment on the product outlined in this document prior to the product being registered for use in Australia. The APVMA will consider all responses received during the public consultation period in deciding whether the product should be registered and in determining conditions of registration and product labelling.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent properties

The chemical active constituent decoquinate has the following properties:

COMMON NAME (ISO):	Decoquinate
CHEMICAL NAME:	Ethyl 6-n-decyloxy-7-ethoxy-4-quinoline-3-carboxylate
CHEMICAL NAME (CAS):	3-quinolinecarboxylic acid, 6-(decyloxy)-7-ethoxy-4-hydroxy-, ethyl ester
PRODUCT NAME (IUPAC):	**DECCOX**
CAS REGISTRY NUMBER:	18507-89-6
EMPIRICAL FORMULA:	$C_{24}H_{35}NO_5$
MOLECULAR WEIGHT:	417.54
PHYSICAL FORM:	Powder
COLOUR:	Cream
MELTING POINT:	242-245°C
STRUCTURAL FORMULA:	

2.2 Product

Dose form: Oral feed additive (premix)

Formulation type: Powder

Level of active: 60 g/kg decoquinate

Physical properties – Appearance: The product is a cream to buff fine powder

Storage and stability

The applicant provided the results of real time and accelerated stability testing conducted using samples stored in the proposed commercial containers. The results indicated that the formulated product is expected to be stable for the duration of the shelf life when stored below 25°C (Air Conditioning) in the proposed commercial packaging.

Packaging

The product will be packaged in 25 kg multi-wall kraft paper bag with polyethylene liner. Based on the storage stability results, the product is not expected to have an adverse effect on the packaging and the packaging is not expected to have an adverse effect on the product.

2.3 Recommendation

The Chemistry and Manufacturing Section[2] of the APVMA evaluated the chemistry and manufacturing aspects of the decoquinate. All of the information (including the physico-chemical properties, spectral identification, manufacturing and quality control aspects, impurity formation, active constituent specification, stability, batch analysis data, analytical methods and packaging information) necessary for the approval of this new active constituent have been provided. The Chemistry and Manufacturing Section is satisfied that the application requirement is met.

[2] This section is previously known as the Pharmaceutical Chemistry Section.

3 TOXICOLOGICAL ASSESSMENT

The Office of Chemical Safety (OCS) within the Department of Health has conducted the toxicology assessment of decoquinate and **DECCOX**.

The toxicological database for decoquinate, which consists primarily of pre-GLP toxicity studies conducted in rats, mice and dogs, did not conform to current OECD Test Guidelines. However, the OCS considered that available data, while of reduced reliability, were sufficient for regulatory purposes.

In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified.

Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. However, from a conservative risk assessment perspective, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies.

Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are generally used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans would be expected.

3.1 Public health aspects and toxicology summary

Decoquinate had low acute oral and inhalational toxicity. Acute dermal toxicity had not been investigated, but is expected to be low, as decoquinate is poorly water soluble, and neither skin irritation nor sensitisation tests showed clinical signs of toxicity. Decoquinate was not a skin or eye irritant in rabbits. The maximisation test in guinea pigs was negative for skin sensitisation.

Decoquinate demonstrated low toxicity following repeat-dosing in dogs and rats; dogs being more sensitive, based on behavioural changes. Although a formal carcinogenic study was not conducted, decoquinate is not carcinogenic. A 2-year study in rats and in dogs found no evidence of an increased incidence of neoplasia. The active constituent did not cause any effects on reproductive parameters in a 3-generation reproduction study in rats. Maternal effects were not observed in developmental studies in rats at the highest test dose. That dose caused minor developmental variations, such as retarded skeletal ossification, in foetal animals. Decoquinate was not teratogenic in rabbits and was negative in a range of *in vitro* mutagenicity/genotoxicity studies. Although one mouse lymphoma forward mutation assay showed equivocal results, the weight-of-evidence indicated decoquinate was not genotoxic.

Data was not available on the formulated product. The acute toxicity of **DECCOX** was estimated from decoquinate and the excipients. **DECCOX** is expected to show low acute toxicity from the oral, dermal and inhalational routes. The product is not expected to be a skin irritant or a skin sensitiser. **DECCOX** contains ingredients which may cause slight mechanical irritation to the eye.

3.2 Occupational health and safety summary

Worker exposure to **DECCOX** during mixing and loading on broiler farms was performed using the Pesticide Handler Exposure Database Surrogate Exposure Guide (1998) modelling. The OCS determined the exposure associated with the handling of **DECCOX** mixed in feed and from administering the treated feed to livestock to be minimal. It is expected that the feed distribution will be largely automated, such as in feeder systems in commercial broiler sheds. Margin of Exposure estimates indicated that the risk from repeat exposure is acceptable. Consequently, specific personal protective equipment for the acute hazards are not required, but safety directions have been recommended to protect against the mechanical acute eye irritation.

As post-application exposure to residues of **DECCOX** is expected to be lower than the exposure during mixing and loading, the risk from re-entry was considered to be minimal. Therefore, a re-entry or re-handling statement was not required for **DECCOX**.

3.3 Evaluation of toxicology

Chemical class

Decoquinate is a 4-hydroxyquinolone anti-protozoal compound. Data from clinical studies suggested decoquinate acts by arresting the development of sporozoites following their penetration of the gut epithelium. Decoquinate significantly inhibited mitochondrial respiration and electron transport in *Eimeria* parasites. However, the mechanism of toxicity is not known.

Toxicokinetics and metabolism

The toxicokinetics studies provided very limited information on the absorption, distribution, metabolism or excretion of this active constituent. Metabolites were found in the tissues of rats fed decoquinate, with highest levels found in the liver and kidney, and only a small amount excreted in the urine (12 per cent in males and 6.4 per cent in females). Most of the recovered radioactivity was the parent compound; three other components were noted in tissues, but not characterised. There was insufficient data to enable a metabolic pathway to be proposed. No dermal absorption data were available for decoquinate.

Acute toxicity

Decoquinate has low acute oral toxicity in the rat (LD_{50} > 5000 mg/kg bw, no deaths) and low acute inhalational toxicity in the rat (4-hr LC_{50} > 4190 mg/m^3, nose-only). Studies on acute dermal toxicity were not provided. The active constituent is virtually insoluble in water/aqueous solutions, is a low acute oral toxicant, and showed no clinical signs of toxicity in skin irritation and sensitisation studies, apart from localised irritation upon intra-dermal injection. As TGAC decoquinate was shown to be of low acute oral toxicity and did not elicit clinical signs of toxicity in skin irritation/sensitisation studies, it was inferred that the acute dermal toxicity may be of comparable acute toxicity, and that the acute dermal hazard associated with TGAC decoquinate exposure is likely to be low. Decoquinate was not irritating to the eye or skin of rabbits and was not a skin sensitiser in guinea pigs.

Acute toxicity studies on **DECCOX** were not provided. The potential acute oral, dermal, and inhalational toxicity, and the eye and skin irritancy and skin sensitisation potential were extrapolated from toxicity data on the active constituent and the excipients. Based on the toxicity estimation, the toxicity profile of **DECCOX** is similar to decoquinate's profile. The product is expected to have low acute oral, dermal and inhalational toxicity. **DECCOX** is not expected to be a skin irritant and a skin sensitiser. It may cause mechanical irritation to the eyes.

Systemic effects

Dogs were more sensitive than rats in short term studies. The lowest NOEL of 15 mg/kg bw/d was established in a 12-week study based on subdued behaviour noted at the LOEL of 62.5 mg/kg bw/d. This behaviour was not reported in the 2-year study in dogs. In an 11-week oral gavage study in rats, decoquinate showed no treatment-related effects. At high doses (> 120 mg/kg bw/d) minor changes in body weight and food consumption were recorded in a 26-week dietary study. Treatment-related systemic toxicity was not noted in long-term studies in rats administered decoquinate at the highest test dose of 37.7 and 48.4 mg/kg bw/d for males and females respectively.

Carcinogenicity

A formal carcinogenicity study was not conducted. The pre-GLP 2-year studies in rat and dog did not show evidence of carcinogenicity. An *in silico* report on the structure of decoquinate suggested that the quinolone component of the structure is indicative of the potential for carcinogenicity. However, the report considered the substitution at the 3-position has greatly reduced this potential. Overall, it was concluded that decoquinate is not likely to be a carcinogen.

Genotoxicity

Decoquinate was tested *in vitro* for genotoxicity in several studies. The weight-of-evidence indicated decoquinate is not genotoxic. In two GLP, non-Guideline Ames tests, decoquinate was not mutagenic. However, the studies tested up to the maximum solubilisation concentration as claimed by the study authors, which was 5.7 µg/plate in one study and 10 000 µg/plate in the other, despite using the same solvent (DMSO). Both studies showed no cytotoxicity and test material precipitation.

Results from a mouse lymphoma forward mutation assay were equivocal for the groups treated with metabolic activation. The highest dose of 2.5 mg/mL showed significantly elevated mutant frequency, but as this group also showed high cytotoxicity, the group was disregarded. At the next lower dose of 2 mg/mL, the mutant frequency was almost double that of the vehicle controls and the mutant frequency showed a rough dose response for those cultures treated with S9.

Decoquinate did not induce chromosomal aberration in Chinese Hamster ovary cells in a chromosome aberration assay. Only three low doses were tested in this study (0, 0.05, 0.15 and 0.25 µg/mL). They were not sufficient to cause cytotoxicity. In a second chromosome aberration assay, a wider range of doses were tested (30, 75.1, 150, 225 and 300 µg/mL). There was no evidence of chromosomal aberration induction, either with or without metabolic activation. The period of exposure of the test substance prior to harvesting was notably different from standard chromosome aberration assay protocols.

In a published journal article (Ohta *et al,* 1980) decoquinate was reported negative (i.e. not mutagenic) in a rec-assay (repair test) and reverse mutation assay.

Reproductive and developmental toxicity

A 3-generation rat reproductive study showed no effects on reproductive parameters. The NOEL of 61 / 71 mg/kg bw/d for M/F was the highest dose tested. Foetal toxicity in the rat developmental study was noted as developmental variations (retarded ossification) at the highest test dose of 300 mg/kg bw/d, while at the same high dose in rabbits there was no evidence of maternal toxicity or a teratogenic effect. A decrease in the mean live foetuses/litter at ≥100 mg/kg bw/d was not ruled out as unrelated to treatment, due to deficiencies in the study and specific endpoints not being reported. The NOEL for foetotoxicity in this study was established at 60 mg/kg bw/d.

3.4 Public health standards

Poisons scheduling

On the 27 June 2013, the delegate to the Secretary to the Department of Health and Ageing decided to include decoquinate in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons with no cut-off. The implementation date was 1 September 2013.

NOEL/ADI

The acceptable daily intake (ADI) for humans is the level of intake of a chemical that can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

An ADI of 0.007 mg/kg bw/d for decoquinate was established in 1969, but details on its determination were not available. The available data were examined to revise the ADI.

Long-term studies in rats and dogs with decoquinate did not establish clear evidence of treatment-related adverse effects. There were no findings of toxicological significance at the highest dose tested. Decoquinate appeared to be of low oral toxicity in all animals tested, with dogs being the most sensitive species. Therefore, the sub-chronic toxicity study in dog was taken as the most appropriate study on which to establish an ADI.

In the 12-week study in dog, subdued behaviour was noted at 62.5 mg/kg bw/d, with the NOEL set at 15 mg/kg bw/d. Based on this NOEL to which a 200-fold safety factor was applied, consisting of factors of 10 each for intra-species and inter-species variation, together with an additional factor of 2 for the database consisting largely of studies conducted prior to GLP and modern standards, the ADI was revised to 0.075 mg/kg bw/d. A correction for oral absorption was not considered appropriate because of the limited metabolism studies available.

ARfD

The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in one meal or during one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

An ARfD for decoquinate was not considered necessary. Data from acute toxicity studies and reproductive/developmental toxicity studies suggested that the acute effects associated with a single exposure to decoquinate are unlikely to present an acute hazard to people.

3.5 Conclusion

The OCS supports the registration of **DECCOX**, containing 60 g/kg decoquinate, for the prevention and control of coccidiosis in broiler chickens.

4 RESIDUES ASSESSMENT

4.1 Introduction

Decoquinate is a coccidiostat that is not currently approved for use in Australia. It is proposed that **DECCOX** be approved for use as a feed additive product for the prevention and control of coccidiosis in broiler chickens. Maximum Residue Limits (MRLs) for decoquinate in edible chicken tissues need to be established to cover the proposed use pattern of **DECCOX**.

One critical radio-labelled total tissue residue decline study was provided, in which chickens were dosed orally with 2 mg [^{14}C]-decoquinate twice daily for seven consecutive days. The dosage was equivalent to that associated with the proposed use of the product. This study was utilised to establish the marker to total residue ratios, to recommend the Maximum Residue Limits and to establish an appropriate withholding period.

4.2 Metabolism

Absorption

Decoquinate was absorbed from the gastrointestinal tract of chickens. Following administration of ^{14}C-decoquinate, plasma concentrations of ^{14}C-decoquinate plateaued within 42 hours of the first treatment. The radiolabelled compound then declined rapidly within 48 hours of the last treatment. Trace amounts remained in the blood and plasma.

Distribution

At 6 hours after the last dose, the highest total radioactive residues (TRR) was found in liver (0.444 mg eq/kg) and kidney (0.411 mg eq/kg). The rank order for total radioactivity in edible tissues was liver>kidney>>>skin/fat>>muscle. The major route of elimination when decoquinate was administered orally to broiler chickens was via excreta.

Metabolism

The data suggested that the metabolism of decoquinate in chickens is limited. Following administration of ^{14}C-decoquinate, tissue residues were characterised as mainly parent decoquinate. In kidney, two major metabolites were found, K1 which accounted for a maximum of 49 per cent of the TRR and K2 which accounted for a maximum of 24 per cent of the TRR. Metabolites corresponding to K1 and K2 were also detected in the liver (L1 and L2). Following derivatisation, metabolites K1/L1 and K2/L2 were tentatively identified as quinolone and hydroxypyridine derivatives of decoquinate.

4.3 Analytical methods

Details of two analytical methods for the analysis of decoquinate in chicken tissue using HPLC were provided. The Limit of Quantification (LOQ) for all chicken tissues (liver, kidney, muscle and skin/fat) were reported to be 0.02 mg/kg for one method and 0.05 mg/kg for the other.

4.4 Residue definition and marker residue

A residue definition for decoquinate as parent decoquinate is currently established in the MRL standard.

The marker residue (parent decoquinate) to total radioactive residues ratios at 2 hours after the final treatment were 0.7, 0.5, 1.0 and 0.9 in liver, kidney, muscle and skin/fat, respectively. The marker residue to total radioactive residues ratios at 6 and 12 hours after the final treatment were quantitatively similar and were 0.9, 0.4, 1.0 and 0.9 in liver, kidney, muscle and skin/fat, respectively.

4.5 Residues in chicken tissues

The critical radio-labelled residue study conducted on chickens involved two daily doses of ^{14}C-decoquinate at 2 mg decoquinate/dose (equal to 4 mg decoquinate/day). The proposed use of **DECCOX** involves a dose concentration of 30 mg decoquinate / kg complete ration. A model broiler chicken in Australia may consume 0.15 kg feed per day on average and therefore may consume 4.5 mg decoquinate per day as a result of the proposed use. Decoquinate residues in chicken liver, kidney, muscle and skin/fat samples were determined at 2, 6 and 12 hours after the last dose. The highest residue levels from those sampling times are relevant to the proposed withholding period of 0 days.

The results of this radio-labelled residue study found the highest upper one-sided 95 per cent confidence limit of the 95th percentile (95/95) residue for parent decoquinate (the marker residue) calculated at each sampling time (2, 6 or 12 hours after the last dose) to be 0.419, 0.268, 0.239 and 0.069 mg/kg in liver, skin/fat, kidney and muscle respectively. The estimated 95/95 tolerance limit for parent decoquinate was 0.61 mg/kg in liver, 0.32 mg/kg in kidney, 0.07 mg/kg in muscle and 0.30 mg/kg in fat at 2 hours after the last dose based on the regression analysis. While the proposed MRLs of 1.0 for liver and skin/fat, 0.8 mg/kg for kidney and 0.5 mg/kg for meat are higher than the residues observed in the trial, they are considered appropriate, noting the size of the dataset available and that they are harmonised with the MRLs established by EFSA. The MRLs are not expected to result in human health concerns based on the conservative JECFA diet.

The proposed withholding period for meat of ‘Zero (0) days’ is supported by the available residue data.

As the proposed use is for broiler chickens and residue data for eggs are not available the proposed restraint ‘DO NOT USE in laying hens’ is supported from a residues perspective. The withholding period (restraint) for eggs of ‘DO NOT USE in chickens which are producing or may in the future produce eggs or egg products which may be used or processed for human consumption’ should be associated with the proposed use.

4.6 Estimated dietary intake

The APVMA utilises the procedure used by JECFA for estimating MRL values, but retains its internally harmonised approach to estimating residue intakes for food safety assessment. The dietary exposure calculation incorporating the JECFA daily food basket represents <2 per cent of the decoquinate ADI.

The chronic dietary exposure to decoquinate is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for decoquinate is equivalent to <1 per cent of the ADI. It is concluded that the chronic dietary exposure of decoquinate is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The Office of Chemical Safety has not established an ARfD for decoquinate and a NESTI calculation is therefore not required.

4.7 Recommendations

The following use pattern is supported from a residues perspective:

ANIMAL	PURPOSE	DOSE RATE
Broiler chicken	For the prevention and control of coccidiosis	Thoroughly mix 0.5 kg / tonne of complete ration to provide 30 mg decoquinate/kg and feed continuously as the only source of feed.

Restraints

DO NOT USE in laying hens.

Withholding periods

MEAT: Zero (0) days

EGGS: DO NOT USE in chickens which are producing or may in the future produce eggs or egg products which may be used or processed for human consumption.

The following amendments are proposed to the MRL standard:

Table 1: MRLs for animal commodities

COMPOUND	FOOD	MRL (MG/KG)
ADD:		
Decoquinate		
	Chicken kidney	0.8
	Chicken liver	1
	Chicken meat	0.5
	Chicken skin / fat	1

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Poultry are currently listed in Part 5B of the APVMA regulatory guidelines as a major export commodity.

5.2 Destination and value of exports

In 2013-14 Australia produced 1,067 kt of chicken meat but only exported 38.4 kt (3.6 per cent of production)[3].

Very little Australian chicken meat is exported. Australian chicken meat is exported primarily to South Africa, the Philippines, Hong Kong, Singapore and the South Pacific islands. The bulk of chicken meat exports have been made up of frozen cuts and edible offal (including any other parts of the chicken that are suitable for human consumption such as feet, liver, kidneys etc)[4].

5.3 Comparison of Australian MRLs with overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits. Codex MRL are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice employed by various countries. Some countries may accept Codex CXLs when importing foods, however decoquinate has not been considered by Codex.

[3] Agricultural commodity statistics 2014: ABARES

[4] Australian Chicken Meat Federation (ACMF) Inc, as published in October 2011: www.chicken.org.au/industryprofile/page.php?id=5.3_Exports

The following relevant international MRLs have been established for decoquinate and it is noted that the residue definition in each jurisdiction is parent decoquinate:

Table 2: International MRLs for decoquinate

COMMODITY	TOLERANCE FOR RESIDUES ARISING FROM THE USE OF DECOQUINATE (MG/KG)							
	AUSTRALIA (PROPOSED)	EU	USA	CANADA	JAPAN	CHINA	TAIWAN	KOREA
Chicken kidney	0.8	0.8	2	2	0.1	2	2	-
Chicken liver	1	1	2	2	0.1	2	2	-
Chicken meat	0.5	0.5	1	1	0.1	1	1	2
Chicken skin/fat	1	1	2	2	2	2	2	-

5.4 Potential risk to trade

It is proposed that decoquinate MRLs at 0.5 mg/kg for meat, 0.8 mg/kg for kidney and 1.0 mg/kg for liver and skin/fat be established, which are the same as those established in Europe and is lower than that established by the USA, China and Taiwan (1 mg/kg for skeletal muscle and 2 mg/kg for other tissues). Codex has not established MRLs for decoquinate and the established Japanese MRLs for chicken kidney, liver and meat (0.1 mg/kg) are lower than those proposed. As the proposed Australian MRLs are equal to or lower than those established by the EU, USA, Canada, China and Taiwan and as the export of chicken meat accounts for <5per cent of total Australian production, the trade risk associated with the proposed use of **DECCOX** is considered to be low.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

Decoquinate (CAS: 18507-89-6) is not listed on Safe Work Australia's Hazardous Substances Information System Database (SWA, 2013). With the available toxicology information, OCS has classified decoquinate as a non-hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). Thus, human health risk phrases will not be required for decoquinate.

Based on toxicology information and concentrations of the active constituent and other excipients in the product, **DECCOX** is not classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

6.2 Formulation, packaging, transport, storage and retailing

Decoquinate will be manufactured overseas. **DECCOX** will be manufactured overseas and imported into Australia as a finished product in 25 kg kraft paper bags with polypropylene liner.

6.3 Use pattern

DECCOX is a premix in an oral powder formulation. It is intended for use in feed to prevent and control coccidiosis in broiler chickens. For broiler chickens, the rate is 0.5 kg **DECCOX**/tonne of feed, sufficient to provide a dose equivalent to 30 mg decoquinate/kg feed. The draft label states that broiler chickens should be fed continuously as the only source of feed from day old to slaughter.

6.4 Exposure during use

Workers in feed mills, poultry farmers and their employees will be the main users of the product. Workers may be exposed when opening bags of **DECCOX**, weighing the product, incorporating it into feed, and transferring and storing the final feed. Workers will be exposed to the product predominately by skin contact as well as inhalation and eye contact during the preparation of stock feed. The product formulation is expected to reduce the amount of dust produced, and hence the workers' inhalational and ocular exposure. Workers dispensing finished feed to livestock will be exposed to the product diluted at up to 0.055 per cent (0.0033 per cent w/w active constituent) on a regular basis.

Occupational exposure studies have not been conducted for decoquinate or **DECCOX**. In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate potential worker exposure during mixing and loading. The exposure associated with handling of mixed product in feed is expected to be minimal and has not been quantitatively estimated in this particular case.

The toxic endpoint and NOEL was derived from a repeat dose study in animals. In this evaluation, a Margin of Exposure (MOE) ≥ 200 was considered acceptable. This MOE took into account both interspecies

extrapolation and intra-species variability and the quality and completeness of the available data on decoquinate.

DECCOX is expected to be a low acute oral and dermal toxicant. The product is not expected to be a skin irritant or a skin sensitiser. Although the formulation is expected to greatly reduce the amount of dust produced, mechanical ocular irritation is possible. The risks associated with repeat worker exposure to **DECCOX** were considered low. Overall, the OCS determined that no specific PPE was necessary, though precautionary statements associated with the potential ocular irritation were considered appropriate.

6.5 Exposure during re-entry

Workers may be exposed to residues of **DECCOX** when clearing away uneaten feed or cleaning equipment. Dermal, inhalational and ocular exposure to dusts may occur during this activity. However, considering that dust formation is reduced and the amount of active constituent in the final feed mix given to broiler chickens is low (30 mg active constituent/kg of feed), the likely level of exposure is considered low and expected to be much lower than exposure during the mixing/loading of the pre-mix product. The risk from re-entry is minimal when the limited re-handling of treated feed and the toxicity profile of decoquinate and **DECCOX** are considered. Therefore, a re-entry or re-handling statement is not required.

6.6 Recommendations for safe use

Users should follow the First Aid Instruction and Safety Directions on the product label. The recommended first aid instruction is, *If poison occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26*. The recommended safety directions are, *May irritate the eyes. Avoid contact with eyes. Wash hands after use*.

6.7 Conclusion

The OCS supports the registration of **DECCOX** for the prevention and control of coccidiosis in broiler chickens. The OCS concludes **DECCOX** can be used safely if handled in accordance with the instructions on the product label. Additional information is available on the product Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

DECCOX is proposed to be applied orally in feeds and fed continuously to chickens at 30 mg ac/kg feed from day old to slaughter.

7.2 Environmental chemistry and fate

Abiotic degradation

Decoquinate contains hydrolysable ester groups, based on its chemical structure. However, it appears from the metabolism of decoquinate in target animals, the majority of the compound is excreted as the unchanged parent compound. This indicates decoquinate is likely to be stable under environmental conditions and ester cleavage is slow.

Biodegradation

Aerobic soil metabolism

The route and rate of degradation of [^{14}C] decoquinate in soil under aerobic condition was investigated in three soil types (sandy loam, loamy sand and clay loam). Soil samples were fortified to a concentration of 1.28 mg/kg. The test was performed in the dark at 20°C in a closed system and volatiles were trapped in ethandiol and ethanolamine. Soil samples were taken over a 120 day period. Decoquinate and its degradation products were separated by HPLC and TLC.

In all soil types, the freely extractable radioactivity was low: <6 per cent in sandy loam, <5 per cent in loamy sand and <9 per cent in clay loam. Radioactivity was associated mainly with the parent compound. Extraction into sodium hydroxide ranged from 36-70 per cent in sandy loam, 47-79 per cent in loamy soil and 24-63 per cent in clay loam with no correlation with time. The combined extracted residue showed that at the end of the study 14 per cent in clay loam, 19 per cent in sandy loam and 32 per cent in loamy soil of AR was the parent compound. After 16 (loamy sand and clay loam) to 32 days (sandy loam) an unknown biodegradation product formed. It increased to 35 per cent in sandy loam, 38 per cent in loamy sand and 35 per cent in clay loam after 120 days. Another unknown biodegradation product was formed up to 5 per cent. In all soil types mineralisation was low; levels of $^{14}CO_2$ after 120 days were <2 per cent. Based on the percent parent compound in the combined extracts, DT_{50}s were estimated to be 96, 140 and 116 days for the three soil types.

Metabolism in animals

A broad range of studies were conducted to evaluate the fate, absorption, distributions, metabolism, and excretion of decoquinate in the target species. Studies were based on the active ingredient either labelled or unlabelled in feed.

In rats receiving [^{14}C]-labelled decoquinate in their diets daily for 11 days, the metabolic plateau based on tissue concentrations of total radioactivity was achieved after 3 days. The major component in each tissue investigated was decoquinate, accounting for up to 43 per cent of the radioactivity in liver and kidney, and 65 per cent in the muscle and skin with 3 metabolites being identified. Male rats excreted 12 per cent of the dose in urine and females excreted 6 per cent in urine. A plateau level of excretion was achieved after 2 days.

The pharmacokinetics and metabolism of decoquinate in poultry was investigated using conventional radiometric methods.

In poultry, decoquinate was eliminated rapidly *via* excreta (mean 90 per cent) within 48 h of the last dose. Tissue residues were low in terms of percentage dose, with liver and kidney together accounted for a mean of 0.12 per cent of the total dose at 24 h post dose. In colostomised chickens, less than 2 per cent of the dose was excreted in urine, indicating a low oral bioavailability. The major component in chicken excreta was confirmed as the parent test material (94 per cent). It was estimated that only 2.6 per cent of the decoquinate dose passing through the broiler chicken is converted or metabolized to non-decoquinate components. The non-decoquinate components have not been identified but are polar in nature.

Mobility

Soil adsorption study

The Koc value of decoquinate was determined experimentally using OECD HPLC methodology. At pH 4.4 and 8.5 decoquinate is determined to have a log Koc >5.6 (Koc >398,107). Based on McCall's Mobility Classifications, decoquinate is considered to be immobile.

Bioaccumulation in aquatic organisms

Based on the metabolism studies, decoquinate is unlikely to be absorbed systemically to allow tissue bioaccumulation to occur by oral administration. Because of the very limited aqueous solubility of decoquinate, the bioaccumulation of decoquinate in fish and aquatic organisms was not measured. This indicated that there will be limited aquatic exposure. Further, the high K_{oc} value indicated that decoquinate is likely to be adsorbed to the soil/sediments. Therefore, under the proposed use pattern, there is little potential for bioaccumulation to occur in aquatic organisms.

7.3 Environmental effects

Aquatic organisms

Acute toxicity studies of decoquinate on rainbow trout (96 h LC50 >0.016 mg ac/L), *Daphnia magna* (48 hr EC50 >0.034 mg ac/L), algae (72 hr ErC50 >0.073 mg ac/L) indicated that decoquinate is not toxic to these species up to its limit of water solubility. At the concentration of 16.3 mg decoquinate/kg dry weight, no effect on survival and development of sediment dwelling larvae of the midge *Chironomous riparius* was observed.

Non-target invertebrates (terrestrial)

Earthworms

The acute toxicity of 14 days LC50 >1000 mg ac/kg soil and the chronic toxicity of 56 days NOEC = 1000 mg ac/kg based on reproduction indicated that decoquinate is very slightly toxic to earthworms, acutely and chronically.

Soil microorganisms

Decoquinate did not have a significant effect on soil microflora, based on respiration and nitrification at concentrations of up to 9.2 mg ac/kg dry soil. It was concluded that decoquinate does not have a long term influence on soil microbial processes.

Phytotoxicity

Decoquinate did not show any effects on the emergence and growth of seedlings of wheat (*Triticum aestivum*), mustard (*Brassica alba*) and mung bean (*Phaseolus aureus*) at concentrations up to 100 mg/kg dry soil. The LC50 for emergence and EC50 for growth were determined to be >100 mg/kg dry soil for each of the species tested. The NOEC was determined to be 100 mg ac/kg soil based on emergence and growth.

7.4 Prediction of environmental risk

Birds

Exposure of birds to decoquinate will be very low, as few species would frequent cultivated areas where manure will be applied.

Aquatic organisms

DotE's environmental risk calculations in the aquatic compartment were based on a worst case pasture scenario with direct excretion into surface water by grazing sheep and cattle, and a worst case run-off in a feedlot situation under Australian farm practices for cattle. As decoquinate is not toxic to aquatic organisms up to its limit of water solubility in the submitted ecotoxicity studies, DotE considered it was not meaningful to calculate a PNEC, nor a risk quotient RQ = $PEC_{surface\ water}$/PNEC. It was concluded that runoff in the feedlot scenario and treated cropland as a result of rainfall event from the use of the proposed product poultry is unlikely to pose an unacceptable risk to the aquatic compartment.

Non-target invertebrates

The proposed use of **DECCOX** under Australian farm practices is not expected to present unacceptable risks to earthworms. This is based on studies showing that the calculated PEC_{soil} was well below the toxicological end point tested for earthworms.

Soil micro-organisms

Decoquinate did not have a significant effect on soil microflora at a concentration of up to 9.2 mg ac/kg dry soil. Based on the worst case soil concentration of 869 µg/kg soil in a poultry shed scenario, the calculated risk quotient indicated that there is unlikely to be an unacceptable risk to soil micro-organisms.

Non-target vegetation

Based on the worst case soil concentration of 869 µg/kg soil in a poultry shed scenario and the EC50 of >100 mg ac/kg dry soil, the risk quotient indicated an acceptable risk to non-target vegetation.

7.5 Conclusion

DotE recommended that the APVMA be satisfied that the proposed use of **DECCOX** on poultry would not be likely to have an unintended effect that is harmful to animals, plants or things, or to the environment under Section 14 subsection 1 of the Agvet Codes.

In order to be satisfied that the proposed uses of the product will not lead to an unintended effect that is harmful to animals, plants or things, or to the environment at the proposed rate and following good agricultural practice, DotE recommended the following amendments to the label particulars:

Protection of Wildlife, Fish and Crustaceans and the Environment

DO NOT contaminate wetlands or watercourses with this product or used containers.

Disposal

Shake and empty contents into medicated feed. Do not dispose of undiluted chemicals on-site. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. Empty bag and left-over product should not be burnt.

8 EFFICACY AND SAFETY ASSESSMENT

Decoquinate is not approved currently for use in a veterinary chemical product. It is an antiprotozoal agent. The product, **DECCOX**, contains 60 g/kg decoquinate and claims to be effective in preventing and controlling coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. mivati*, *E. maxima* and *E. brunetti* in broiler chickens. The label instructs the mixing of 500 g **DECCOX** in each tonne of complete feed to provide 30 mg decoquinate/kg feed (30 ppm) and feeding the medicated feed to broiler chickens continuously as the only source of feed from day old to slaughter. The product is prohibited from administration to chickens which are producing or may in the future produce eggs or egg products which may be used or processed for human consumption.

8.1 Evaluation of efficacy data

The efficacy data included results of decoquinate against artificial infection of single or mixed species of the target pathogens in floor pen/battery trial and field situations.

The trial designs, treatment group sizes, ages of chickens used, experimental conditions, administration of test and reference products, sample collection and analysis of data were generally appropriate for establishing the efficacy and margin of safety of the test product under normal use conditions.

In nine dose determination studies in broiler chickens, decoquinate at inclusions greater than 30 ppm was more effective than at inclusions equal to or lower than15 ppm in controlling each of the target *Eimeria* spp.

In five dose confirmation studies in broiler chickens, decoquinate administered in-feed at 20, 30 and 40 ppm post challenge was effective in arresting sporozoites of *Eimeria*, compared to salinomycin and robenidine. Each dose was effective, with 30 ppm and 40 ppm being most effective against all of the target species. Some sporozoites of *E. maxima* were able to progress to gametocytes before degenerating.

One floor pen and one battery trial assessed decoquinate at 30 ppm when fed to broiler chickens prior to the birds being inoculated with mixed species of *Eimeria*. The coccidiostat was effective against each *Eimeria* species, compared to untreated, uninfected controls and untreated, infected controls.

In a confirmatory field study conducted in Australia in broiler chickens, **DECCOX-**medicated feed at 30 ppm was effective against an artificial infection of Australian species of *Eimeria*, compared with untreated controls and positive controls.

Results of three microbiological studies of *E. tenella* and *E. necatrix* in chickens suggested the potential of *Eimeria* exists to develop resistance to decoquinate under practical field usage in intensive animal production. Resistance was evidence after relatively few passages.

Claims of efficacy against *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. mivati*, *E. maxima* and *E. brunetti* are supported when **DECCOX** is administered in-feed at 30 ppm and fed continuously from day old to slaughter to broiler chickens.

8.2 Evaluation of target animal safety data

Three target animal safety studies were conducted in which male and female broilers were fed decoquinate continuously at inclusions of 15, 30, 40, 90, 150 and 300 ppm for several weeks. Except for males in the 30 ppm group, weight gains and feed efficiency were greater than controls. No adverse effects were recognised pathologically in organs that could be attributed to treatment. Abnormal clinical signs were not evident. At 400 ppm, feed and water intakes were not affected adversely, although the chickens consumed more feed and water. Haematological findings in treated groups were not different to controls, but biochemical findings were different.

In two other studies, decoquinate showed no detrimental effects when fed continuously at 40 ppm for a longer period to male and female broiler breeders.

In acute oral toxicity studies, broiler chickens showed no gross visible lesions at necropsy after being administered doses of 1 g/kg or 5 g/kg body weight decoquinate once by gavage. Chicks showed no effects over 7 days to one oral treatment of 0.11, 1.1 or 11 g decoquinate/kg bw. In contrast, 3200 ppm decoquinate in-feed depressed growth of chickens for 31 days within 7 days of the birds being fed in a sub-acute study. Males had lower white blood cell counts and heterophil count increased in females.

In chronic toxicity studies, there were no macroscopic or histopathologic drug effect caused by inclusions of 75, 80, 160, 750, 800 and 1600 ppm decoquinate fed to chickens for up to 180 days. Differences in heterophils and white cell counts were not considered significant. In another chronic toxicity study, day old chicks tolerated decoquinate fed at 10,000 and 100,000 ppm in rations for 28 days. The main observed effect was a decrease in testes weights in chicks in the 100,000 ppm treatment group. At 64 days, treated chicks had lowered haematological values for PCV, WBC and lymphocyte counts, and pale, clay-like faeces.

8.3 Conclusions

Under normal use conditions, **DECCOX** is effective in preventing and controlling *Eimeria* infections in broiler chickens. It should be noted that decoquinate does not provide a therapeutic level of control of all endogenous stages of the life cycle of *Eimeria*. Tolerance/safety studies have shown that broiler chickens tolerated the product at very high inclusions and that the product has a very wide margin of safety in the event of over-dosage.

9 LABELLING REQUIREMENTS

Signal heading:	**CAUTION** **KEEP OUT OF REACH OF CHILDREN** **FOR ANIMAL TREATMENT ONLY**
Product name:	**DECCOX®**
Active constituent:	Decoquinate 60g/kg
Statement of claims:	**For the prevention and control of coccidiosis in broiler chickens – caused by** ***Eimeria tenella, E. necatrix, E. acervuline, E. mivati, E. maxima*** **and** ***E. brunetti*****.**
Net contents:	**25 kg**
Directions for Use Heading:	**DIRECTIONS FOR USE:**
Restraints:	**DO NOT USE in laying hens**
Precaution	**USE with caution in feeds containing bentonite**. DECCOX should not be mixed with rations containing bentonite. Bentonite is a type of clay that is used as a compacting and dispersing agent in some feeds. This is not because bentonite interferes with the activity of DECCOX in the feed, but because it interferes with the assay method. Simply put, samples of feed containing bentonite and DECCOX would not assay properly. Therefore, feed formulations containing bentonite should be avoided.
Dosage & administration:	**Mixing Directions: Must be thoroughly mixed with other feed ingredients at the following rates:** **Prevention and control of coccidiosis** **Broiler chickens** Thoroughly mix 0.5kg/tonne of Deccox in each tonne of complete ration to provide 30mg decoquinate per kilo and feed continuously as the only source of feed from day-old to slaughter.
General directions:	General advice is not to use the same in-feed anticoccidial for extended periods, to rotate among different classes of ionophores and to rest each product periodically. Use of a synthetic or chemical product once a year is recommended to clean up field strains.

Withholding Periods	**MEAT: Zero (0) days** **EGGS**: **DO NOT USE in chickens which are producing or may in the future produce eggs or egg products which may be used or processed for human consumption**
Safety Directions:	May irritate the eyes. Avoid contact with eyes. Wash hands after use.
Environmental Protection Statement:	**Protection of Wildlife, Fish and Crustaceans and the Environment** DO NOT contaminate or wetlands or watercourses with this product or used containers.
First Aid:	If poisoning occurs, contact a doctor or Poisons Information Centre. *Phone Australia 131126.*
Disposal:	Shake and empty contents into medicated feed. Do not dispose of undiluted chemicals on-site. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. Empty bag and left-over product should not be burnt.
Storage:	Store below 25°C (Air Conditioning).

The following is for APVMA use only:

APVMA approval no.	**66670/54134**

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ARfD	Acute Reference Dose
bw	bodyweight
d	day
DT_{50}	Time taken for 50% of the compound to dissipate
EC_{50}	concentration at which 50% of the test population are immobilised
ErC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
ESI	Export Slaughter Interval
Eq	equivalent
Fo	original parent generation
g	gram
GLP	Good Laboratory Practice
hr	hour
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
kt	kilotonne
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
LOD	Limit of Detection – level at which residues can be detected
LOEL	Lowest Observable Effect Level
LOQ	Limit of Quantitation – level at which residues can be quantified

M/F	male/female
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
NOEC/NOEL	No Observable Effect Concentration Level
PCV	pack cell volume
PEC	predicted environmental concentration
PNEC	predicted no effect concentration
PPE	Personal Protective Equipment
ppm	parts per million
RBC	Red Blood Cell Count
TGAC	Technical grade active constituent
TLC	thin layer chromatography
TRR	Total Radioactive Residues
µg	microgram
WBC	White Blood Cell Count
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Leaching	Removal of a compound by use of a solvent
Metabolism	The chemical processes that maintain living organisms
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

National Occupational Health and Safety Commission 2004, NOHSC Approved Criteria for Classifying Hazardous Substances.