Australian Government
Department of Health and Ageing
NICNAS

Existing Chemical
Secondary Notification Assessment
NA/467S

N-(n-butyl) thiophosphoric triamide (NBPT)

February 2011

National Industrial Chemicals Notification and Assessment Scheme
GPO Box 58, Sydney NSW 2001, Australia www.nicnas.gov.au

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are conducted in conjunction with the Australian Government Department of Sustainability, Environment, Water, Population and Communities which carries out the environmental assessment.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health and/or environmental effects.

Chemicals that have been assessed as new or existing chemicals may require a reassessment of the risk of the chemical under the secondary notification provisions of the Act.

This assessment report has been prepared by the Director of NICNAS, in accordance with the secondary notification provisions of the Act. Under the Act manufacturers/importers of the chemical are required to notify the Director of new information and apply for assessment. New information can include an increase in quantity imported, the commencement of Australian manufacture, increased environmental exposure, and/or additional information becoming available on hazards, as is the case of N-(n-butyl) thiophosphoric triamide (NBPT).

Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made appear in the Commonwealth Chemical Gazette.

In accordance with the Act, publication of this report revokes the declaration of this chemical for secondary assessment, therefore manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under Section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of assessment reports for new and existing chemical assessments are freely available from the web (www.nicnas.gov.au).

Copies of this and other assessment reports are available on the NICNAS website. Hardcopies are available from NICNAS from the following address:

GPO Box 58, Sydney,
NSW 2001, AUSTRALIA
Tel: +61 (02) 8577 8800
Freecall: 1800 638 528
Fax: +61 (02) 8577 8888

Other information about NICNAS (also available on request) includes:

- NICNAS Service Charter;
- Information sheets on NICNAS Registration;
- Information sheets on Priority Existing Chemical and New Chemicals assessment programs;
- Safety information sheets on chemicals that have been assessed as Priority Existing Chemicals;
- Details for the NICNAS Handbook for Notifiers; and
- Details for the Commonwealth Chemical Gazette.

More information on NICNAS can be found at the NICNAS web site:

http://www.nicnas.gov.au

Other information on the management of workplace chemicals can be found at the following web site:

http://safeworkaustralia.gov.au

Overview and Recommendations

Overview

N-(n-butyl) thiophosphoric triamide (NBPT), CAS No. 94317-64-3, was assessed by NICNAS in 1997 as a new chemical (NA/467) and is now listed in the Australian Inventory of Chemical Substances (AICS). In June 2009, additional data on NBPT was provided that warranted secondary notification. This secondary notification assessment focuses on the new data provided.

NBPT is a urease inhibitor which can reduce nitrogen loss by ammonia volatilisation from urea. It is used as a fertiliser additive in agricultural applications.

Manufacture and importation

NBPT is not manufactured in Australia. AGROTAIN® containing 20% NBPT is imported to Australia in sealed containers and transported to approximately 20 centres for reformulation. Import volume of NBPT is approximately 4.24 tonnes per year.

Uses

In Australia, AGROTAIN® is used in combination with granular urea or urea ammonium nitrate (UAN) liquid fertilisers. AGROTAIN® is added to fertilisers to achieve a concentration of 0.053% to 0.064% NBPT in granular urea, and 0.038% concentration in UAN.

Health effects

Oral absorption of NBPT is almost complete. No information is available on absorption via dermal or inhalation routes. After absorption, NBPT is distributed to various organs in animals, and NBPT concentrations in the blood stream decrease following a biphasic pattern. After a single oral dosing, more than 80% of the given dose was excreted in 7 days, mainly via expired air (35%), urine (24%) and faeces (9%). From the urine samples, two major metabolites of NBPT were identified, N-(n-butyl)-thiophosphoric diamide and the glucuronic acid conjugate of NBPT.

NBPT is of low acute oral and dermal toxicity in rats. No inhalation toxicity data for NBPT are available. NBPT is neither a skin irritant in rabbits nor a skin sensitiser in guinea pigs. However, NBPT produced severe eye irritant effects in a rabbit study.

NBPT showed little evidence of mutagenicity in two Ames tests with and without metabolic activation. An in vivo mouse micronucleus study was negative for evidence of clastogenicity.

Repeated dose studies in animals at high doses showed changes in animal bodyweights and bodyweight gains, liver and kidney weights with histopathological evidence at necropsy, and changes in biochemical assay results. In addition, salivation and languid behaviour, decreased erythrocyte cholinesterase levels and lower grip strength were observed at high doses. The repeated dose NOAEL for males is 74 mg/kg bw/d based on liver effects and changes in neurobehaviour and haematology and the LOAEL is considered to be 377 mg/kg

bw/d. A NOAEL could not be determined in females in the study, but the LOAEL for females is 17 mg/kg bw/d based on effects seen in the uterus.

NBPT caused weight changes in reproductive organs with histopathological findings in both males and females, and abnormalities in sperm evaluations. The NOAEL in males is 21 mg/kg bw/d based on decreased sperm motility with epididymal lesions at 84 mg/kg bw/d, and the NOAEL in females is 17 mg/kg bw/d based on increased uterine weight at 88 mg/kg bw/d (from the 90-day repeat-dose study).

Developmental toxicity of NBPT was investigated in both rats and rabbits and no obvious adverse effects were observed in these prenatal developmental toxicity studies. Decreased bodyweight gain was seen in the two-generation study at the highest dose (362 mg/kg bw/d) at which maternal toxicity was also reported. Systemic toxicity (reduced bodyweight gain) was seen in all generations and considered to be secondary to maternal toxicity. The NOAEL for developmental toxicity was not determined.

Occupational exposure and health risk

Imported AGROTAIN® formulation is transported to reformulating facilities for reformulation into granular urea fertilisers. Occupational exposure during transport, unloading and warehousing of AGROTAIN® is limited to accidental release and any subsequent exposure. Potential occupational exposure to NBPT is possible during manual handling of AGROTAIN® at the reformulation sites, and to a lesser extent during fertiliser application.

Serious damage to the eyes is a concern for workers handling AGROTAIN® containing 20% NBPT. Risk of adverse systemic toxicity is considered to be low. NBPT adversely affects rat reproductive organs and there is a potential risk of effects on fertility with prolonged exposure to preparations containing $\geq 5\%$.

The final fertiliser preparations containing 0.038% to 0.064% NBPT are not classified as hazardous based on the percentage of NBPT content. However, caution should be taken to avoid repeated or prolonged eye contamination of NBPT. Dermal exposure for applicators during spray application is estimated by the US EPA's Pesticide Handlers Exposure Database (PHED) to be 0.0069 mg/kg bw/d which indicates that the health risk for applicators is low.

Public exposure and health risks

No public exposure occurs during the reformulation or application processes.

NBPT may be absorbed by crops grown on treated soil. Residues of the chemical in food commodities are expected to be negligible. Leaching into groundwater from the soil is expected to be low.

Environmental effects

The ecotoxicity data for the substance indicates that NBPT is practically non-toxic to bluegill (*Lepomis macrochirus*) (LC50=1140 mg/L), water flea (*Daphnia magna*) (EC50=290 mg/L) and algae (*Selenastrum capricornutum*) (EC50=280 mg/L).

While no specific tests had been conducted on soil invertebrates, the notifier stated that no adverse effects on earthworms had been reported during widespread field trials with AGROTAIN®.

Similarly, no avian toxicity studies had been conducted, although the notifier has provided some figures from a pilot metabolism study in which 250 mg/kg ^{14}C- NBPT was administered to laying hens. The results of this indicated an LD50 >50 mg/kg in hens.

Environmental exposure and risks

During reformulation, a hood cover is used to catch any product drift, and spray operations are conducted in an enclosed building. Any residues that do remain in the mixing equipment and drums are rinsed off with water, and are likely to enter the sewer. Residues are minimal and drums are either sent to secure landfill, or recycled.

During end use, NBPT is applied directly to soil with the application of the fertiliser at a rate of 0.046 kg/ha of NBPT. There is no home garden use of this product.

Because most NBPT is applied under the surface, exposure to birds is reduced. No data are available on NBPT toxicity to soil vertebrates. The fast rate of mineralisation in and ability of NBPT to bind to soil would limit the extent of NBPT leaching to groundwater.

The worst case predicted environmental concentrations (PEC) of 0.68 ppm in a country sewer treatment plant and 3.1 ppb in a body of water are several orders of magnitude lower than the most sensitive observed effect of EC50=280 ppm to algae. Hazard to aquatic species through reformulation and end use is expected to be low.

Recommendations

This section provides the recommendations arising from the secondary notification assessment of NBPT. The recommendations provided by the new chemical assessment report (NA/467) are still applicable.

Recommendations are directed principally at regulatory bodies and importers and reformulators of NBPT products. Implicit in these recommendations is that best practice is implemented to minimise occupational and public exposure and environmental impact.

Recommendations to National Bodies

Safe Work Australia

NBPT is currently not listed in Safe Work Australia's Hazardous Substances Information System (HSIS). Based on the toxic effects of NBPT, it is recommended that NBPT be listed in the HSIS.

In accordance to the *Approved Criteria in Classifying Hazardous Substances* (NOHSC 2004), NBPT is classified as:

- R41 Risk of serious eye damage
- R62 Possible risk of impaired fertility (Toxic to reproduction, Category 3)

The concentration cut-offs for products/mixtures containing NBPT are:

Risk Phrases*	Concentration Cut-off
Xn, R62; R41	Concentration ≥ 10%
Xn, R62; R36	5% ≤ Concentration < 10%

* Xn = Harmful
R36 = Irritating to eyes

The following safety phrases are also recommended:

- S25 Avoid contact with eyes
- S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
- S36/37 Wear suitable protective clothing and gloves
- S39 Wear eye/face protection

This classification should be reflected in Safe Work Australia's HSIS and should be adopted by industry on publication of this report.

Recommendations to importers and state and territory governments

Hazard Communication – Material Safety Data Sheets

Under the *National model regulations for the control of workplace hazardous substances* (NOHSC, 1994b) and the commonwealth, state and territory regulations introduced in accordance with these national model regulations, employees shall have ready access to Material Safety Data Sheets (MSDS) for hazardous substances at their workplace. MSDS provide information to those who use the hazardous substance.

It is recommended that importers of NBPT review their MSDS for compliance with the *National code of practice for the preparation of material safety data sheets, 2nd edition* (NOHSC, 2003) paying particular attention to the hazard classification in the recommendation above. The MSDS should be provided to the occupational health and safety officer during the workplace assessment process.

A copy of the MSDS should be easily accessible to employees.

It is recommended that state and territory occupational health and safety authorities monitor for compliance with the requirements.

Hazard Communication – Labels

In accordance with the *National code of practice for the labelling of workplace substances* (NOHSC, 1994a) it is recommended that importers of NBPT review their labels for compliance and pay particular attention to the following:

In addition to the hazard classification risk phrases it is recommended the safety phrases above be incorporated on labels of NBPT or of products containing NBPT in concentrations greater than or equal to 5%.

It is recommended that states and territories monitor for compliance with the requirements.

Recommendations from the previous assessment of NBPT as a new chemical

Occupational Controls

Employers should implement the following safe work practices and engineering controls to minimise occupational exposure during handling of NBPT:

- Workers should have adequate education and training before handling NBPT.
- Good personal hygiene should be practiced to minimise the potential for ingestion, direct skin or eye contact with NBPT.

- Employers should ensure dust concentration at workplaces is below the exposure standard of 10 mg/m^3 (*National exposure standards for atmospheric contaminants in the occupational environment* (NOHSC, 1995)).
- Avoid spills and splashing during use. Any spillages should be cleaned up promptly with absorbents which should then be put into containers for disposal.

Employers should ensure that the following personal protective equipment are used by workers to minimise occupational exposure to NBPT:

- Safety goggles should be selected and fitted in accordance with Australian Standard (AS) 1336 (Standards Australia, 1994).
- Industrial clothing should conform to the specifications detailed in AS 2919 (Standards Australia, 1987) and AS 3765.1 (Standards Australia, 1990).
- Impermeable gloves or mittens should conform to AS 2161 (Standards Australia, 1978).
- Occupational footwear should conform to AS/NZS 2210 (Standards Australia/Standards New Zealand, 1994).
- After exposure, contaminated PPE should be thoroughly cleaned before re-use.

If products and mixtures containing NBPT are classified as hazardous to health in accordance with the *Approved criteria for classifying hazardous substances* (NOHSC, 2004) workplace practices and control procedures consistent with provisions of state and territory hazardous substances legislation must be in operation.

Secondary Notification

Under the Act, secondary notification of NBPT may be required where an applicant or other introducer (importer) of NBPT becomes aware of any circumstances that may warrant a reassessment of its hazards and risks. Specific circumstances include:

a. The use of NBPT has changed or is likely to change significantly.

b. Manufacture of NBPT has begun or is likely to begin in Australia.

c. Additional information has become available on the adverse health and/or environmental effects of NBPT.

d. Importation of another form of NBPT that may impact on occupational risk occurs.

The Director must be notified within 28 days of the introducer becoming aware of any of the above circumstances.

Acronyms and Abbreviations

ALT	alanine aminotransferase – also known as glutamic pyruvic transaminase (GPT)
AP	alkaline phosphatase
AST	aspartate transaminase - also known as glutamic oxaloacetic transaminase (GOT)
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetre
CO_2	carbon dioxide
d	day
DSEWPC	Australian Government Department of Sustainability, Environment, Water, Population and Communities
EC	European Commission, or European Community
EC50	median effective concentration
g	gram
GD	gestation day
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GLP	good laboratory practice
ha	hectare
kg	kilogram
L	litre
LC50	median lethal concentration
LC/MS	liquid chromatography-mass spectrometry
LD50	median lethal dose
LOAEL	lowest-observed-adverse-effect level
m	metre
mg	milligram
MOE	margin of exposure
MSDS	material safety data sheet
NBPT	N-[n-butyl] thiophosphoric triamide

ND	new data
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NMR	nuclear magnetic resonance spectroscopy
OECD	Organisation for Economic Cooperation and Development
PEC	predicted environmental concentration
PHED	Pesticide Handlers Exposure Database
PND	postnatal-day
PPE	personal protective equipment
QA	quality assurance
TG	test guidelines
UAN	urea ammonium nitrate
US EPA	United States Environmental Protection Agency

1. Introduction

1.1 Background

N-[n-butyl] thiophosphoric triamide (NBPT), CAS No. 94317-64-3, was assessed as a new chemical (NA/467) in 1997 under Section 23 of the *Industrial Chemicals (Notification and Assessment) Act, 1989* (the Act). NBPT is now listed in the public section of the Australian Inventory of Chemical Substances (AICS). The Full Public Report of NBPT is available on the NICNAS website:

www.nicnas.gov.au/publications/CAR/new/NA/NAFULLR/NA0400FR/NA467FR.pdf

NBPT, a urease inhibitor which can reduce nitrogen loss by ammonia volatilisation from urea, is used as a fertiliser additive in agricultural applications.

NBPT is not manufactured in Australia, but has been imported into Australia at 25% in a liquid formulation called AGROTAIN®. The product was reformulated in Australia to a final maximum concentration of 0.2%-0.3% NBPT with other ingredients such as granular urea or urea ammonium nitrate. The end-use product is either broadcasted (scattered) or applied to the subsoil by farmers/applicators.

At the time of assessment as a new chemical toxicological studies were provided for NBPT and the report classified the chemical as hazardous on the basis of an eye irritation study on the imported commercial formulation AGROTAIN®.

In August 2008, NICNAS was advised of the intention to introduce to Australia two dry formulations containing NBPT. Additional data on NBPT including new data on physicochemical properties, toxicokinetics, irritation, repeated dose and reproductive studies were also provided.

In June 2009, the unavailability of acute inhalation studies at that stage prompted the withdrawal of the intention to import the dry formulations to Australia.

Additional data was also provided on import volume and NBPT concentration in AGROTAIN® during reformulation in Australia.

The new toxicological data provided warrant reassessment of NBPT and as the chemical is listed on the AICS, this chemical is now being assessed as an existing chemical under section 68A of the Act, covering secondary notifications of existing chemicals.

Data submitted for the original assessment on use, exposure and animal toxicity are summarised in this report in the relevant sections. Details of the studies provided for asssessment as a new chemical are reproduced in Appendix I. New data submitted for this assessment are discussed in detail and identified by the abbreviation **ND**.

1.2 Declaration

A notice was published in the *Chemical Gazette* of June 2009, requiring a secondary notification of NBPT in accordance with Section 65(2) of the Act. The declaration of this secondary notification concerned the introduction of new

formulations and additional data provided that have relevance to the hazardous nature of NBPT and occupational exposure in Australia to NBPT.

The declaration required the provision of any information relevant to an assessment of NBPT which was not originally covered in the 1997 assessment as a new chemical.

New data provided for this secondary notification include the following documents:

- NBPT: Determination of general physicochemical properties (SafePharm Laboratories, 2001a);
- NBPT: Determination of hazardous physicochemical properties (SafePharm Laboratories, 2001b);
- Determination of melting point/melting range for butyl phosphorothioic triamide (NBPT) (ABC Laboratories, 2001a);
- Determination of flammability for butyl phosphorothioic triamide (NBPT) (ABC Laboratories, 2001b);
- Determination of n-octanol/water partition coefficient (shake flask method) for butyl phosphorothioic triamide (NBPT) (ABC Laboratories, 2001c);
- Metabolism of [^{14}C] NBPT in male Sprague-Dawley rats (Ricerca, 1997);
- NBPT: Acute eye irritation in the rabbit (SafePharm Laboratories, 2001c);
- NBPT: Toxicity to rats by dietary administration for 13 weeks incorporating a neurotoxicity screen (Huntingdon Life Sciences, 1997);
- N-(n-butyl) thiophosphoric triamide (NBPT) A study of the effect on pregnancy of the rat (gavage administration) (Huntingdon Research Centre, 1995a);
- N-(n-butyl) thiophosphoric triamide (NBPT) A Study of the effect on pregnancy of the rabbit (gavage administration) (Huntingdon Research Centre, 1995b);
- NBPT: Study of reproductive performance in CD rats treated continuously through two successive generations by dietary administration (Huntingdon Life Sciences, 1999); and
- an accident report submitted to the US EPA of 2 workers handling AGROTAIN® product in a New Zealand factory in 2006 (as reported by the overseas manufacturer).

1.3 Objectives

The objectives of this assessment are to review the new data made available since the publication of the 1997 new chemical assessment report (NA/467), and where appropriate, revise the original assessment to:

- characterise the hazards of NBPT to human health;
- characterise potential occupational and public exposure to NBPT;
- characterise risk of adverse effects resulting from exposure to workers and the general public; and

- make appropriate recommendations to control exposures and/or reduce potential health risks for workers and the general public.

No new environmental studies for NBPT were provided and reassessment of the environmental risk has not been conducted. Some estimations were revised due to new data on import volume and NBPT concentration in AGROTAIN® provided during the secondary notification. These changes do not alter the conclusions of the environmental risk assessment.

1.4 International perspective

NBPT is subject to a US EPA Significant New Use Rule (SNUR) codified in 40 CFR § 721.6090 in accordance with the Toxic Substance Control Act (TSCA). NBPT is also subject to a Section 5(e) consent order based on the anticipated large-scale exposure, and Section 12(b) export notification obligations.

AGROTAIN® containing 20%-25% NBPT has been approved under the Canadian *Fertilizer Act*. All components are on the Canadian Domestic Substances List (DSL). According to the Canadian Workplace Hazardous Materials Information System (WHMIS) from the Canadian Centre for Occupational Health and Safety, it is classified under Class D (Poisonous and Infectious Material), Division 2, Subdivision B (Toxic material).

1.5 Peer review

During all stages of preparation, this report has been subject to internal peer review by NICNAS.

1.6 Applicant

Following the Secondary Notification declaration of NBPT, one company applied for assessment of this chemical.

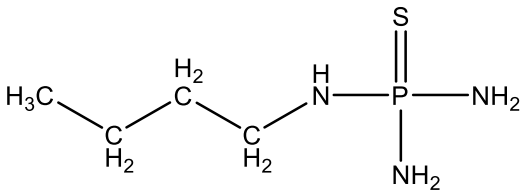
In accordance with the *Industrial Chemicals (Notification and Assessment) Act 1989*, NICNAS provided the applicant with a draft copy of the report for comment during the corrections/variations phase of the assessment. The applicant details are as follows:

Quinfert Pty Ltd
9a Hamilton St
Gisborne VIC 3437

2. Chemical Identity, Physical and Chemical Properties

Chemical identity, physical and chemical data assessed by NICNAS in NA/467 (NICNAS, 1997) are reproduced in this report with new data indicated as **ND**.

2.1 Chemical identity

Chemical Name:	N-(n-butyl) thiophosphoric triamide (NBPT)
Chemical Abstracts Service (CAS) Registry No.:	94317-64-3
Other Names:	phosphorothioic triamide, butyl- butylphosphorothiotriamide n-butylthiophosphoric triamide NBPT BTPT TPT UL6 NBPTP BNPS
Trade Name:	AGROTAIN® (containing 20% NBPT, **ND**)
Molecular Formula:	$C_4H_{14}N_3PS$
Structure Formula:	
Molecular weight	167.2
Method of Detection and Determination:	HPLC with UV detection (PTRL West, 1996c)
Spectral Data:	The submission included ^{13}C, ^{31}P and ^{1}H NMR spectra of NBPT.

2.2 Physical and chemical properties

Property	Value	Method/Comment
Appearance at 20°C & 101.3 kPa	White crystalline solid	
Boiling point	264.0°C [calculated value] (**ND**)	Differential scanning calorimetry, Method A2 of Commission Directive 92/69/EEC (SafePharm Laboratories, 2001a)
Melting point	59.1°C (**ND**)	OECD TG 102 (ABC Laboratories, 2001a)
Density	1223.2 kg/m^3 at 20.0±0.5°C (**ND**)	Gas comparison pycnometer, Method A3 of Commission Directive 92/69/EEC (SafePharm Laboratories, 2001a)
Vapour pressure	1.067 kPa at 40°C	
Water solubility	4.3 g/L at 25°C	PTRL West, 1996a
Partition co-efficient (n-octanol/water)	log P_{ow}=0.444 (**ND**)	ABC Laboratories, 2001c
Surface tension	49.4 mN/m at 22.0±0.5°C (**ND**)	Method A5 of Commission Directive 92/69/EEC (SafePharm Laboratories, 2001a)
Hydrolysis as a function of pH	T1/2 at pH 3.0=58 minutes at 25°C T1/2 at pH 7.0=92 days at 25°C T1/2 at pH 11.0=16 days at 25°C	PTRL West, 1996b
Adsorption coefficient	Koc<17.8 at pH 5.5 Koc<17.8 at pH 8.5 (**ND**)	OECD TG 121 (SafePharm Laboratories, 2001a)
Dissociation constant	Not determined	
Particle size	0.199% (proportion of material having a particle size less than 100 µm) (**ND**)	Sieve method designed to comply with a European Commission technical guidance document June

		1996 (SafePharm Laboratories, 2001a)
Flash point	96°C (closed cup)	
Flammability	Not considered highly flammable (**ND**)	Method A10 of Commission Directive 92/69/EEC (ABC Laboratories, 2001b)
Autoignition temperature	376 ± 5°C (**ND**)	Method A15 of Commission Directive 92/69/EEC (SafePharm Laboratories, 2001b)
Relative self-ignition temperature for solid	None below its melting temperature (**ND**)	Method A16 of Commission Directive 92/69/EEC (SafePharm Laboratories, 2001b)
Oxidising properties	Predicted negative based on NBPT chemical structure (**ND**)	Method A17 of Commission Directive 92/69/EEC (SafePharm Laboratories, 2001b)
Explosive properties	Predicted negative based on NBPT chemical structure (**ND**)	Method A14 of Commission Directive 92/69/EEC (SafePharm Laboratories, 2001b)
Reactivity/stability	Stable and unreactive at normal temperatures	

Comments on physicochemical properties

Boiling point was calculated using the Stein and Brown method. The test material volatilised during decomposition leaving a crystalline residue and the thermograms showing gradual decomposition. Volatilisation with decomposition meant that no value for the boiling temperature could be determined experimentally (**ND**).

Hydrolysis data indicate that hydrolysis could be an important breakdown mechanism for this chemical under very acidic conditions and less so at pH 7, though the rate at the extremes of the normal environmental pH range (5-9) is unclear.

The surface tension study showed NBPT being a surface-active material. The study report indicated that some impurities in NBPT could be contributing to or responsible for the test results as the purity of the test material is approximately 94% (**ND**).

Flammability of NBPT was determined by a preliminary test according to EC Directive 92/69/EEC A.10 Flammability. NBPT was moulded into an unbroken strip 250 mm long by 20 mm wide by 10 mm high on an aluminium base plate. A propane torch flame was applied to one end of the test substance. After 2 minutes, the flame was removed and the test substance was observed for an additional 2 minutes. Since NBPT did not burn or smoulder for a distance of 200 mm within 4-

minute test period, no further testing of flammability was required and NBPT was not considered highly flammable (**ND**).

2.3 Composition

2.3.1 Technical grade NBPT

Degree of Purity: 85%

Toxic or Hazardous Impurities

Chemical name: Tetrahydrofuran (CAS No.: 109-99-9)
Weight percentage: 0-2%
Toxic properties: The HSIS classification includes: F (Highly flammable), R11 (Highly flammable), R19 (May form explosive peroxides), and Xi (Irritant), R36/37 (Irritating to eyes and respiratory system).

Chemical name: Triethylamine (CAS No.: 121-44-8)
Weight percentage: 0-2%
Toxic properties: The HSIS classification includes: F (Highly flammable), R11 (Highly flammable), C (Corrosive), R35 (Causes severe burns), and Xn (Sensitising), R20/21/22 (Harmful by inhalation, in contact with skin and if swallowed).

Non-hazardous Impurities (> 1% by weight):

Chemical name: N,N-di-(n-butyl) thiophosphoric triamide (DNBPT)
Weight percentage: 0-3%

Chemical name: N,N,N-tri-(n-butyl) thiophosphoric triamide (TNBPT)
Weight percentage: 0-1%

Chemical name: thiophosphoric triamide (TPT)
Weight percentage: 0-3%

Chemical name: Other (e.g. dimers and more complex materials)
Weight percentage: 0-10%

2.3.2 AGROTAIN®

Content of NBPT: 20% (**ND**)

The formulation AGROTAIN® contains 25% NBPT, 60%-65% of unspecified non-hazardous ingredients, and 15% of N-methyl pyrrolidone. N-methyl pyrrolidone (CAS No. 872-50-4) is toxic to reproduction (T, R61), an irritant (Xi, R36/37/38) and has an exposure standard of 25 ppm or 103 mg/m^3 (TWA) in the HSIS. The threshold for classification of a mixture containing N-methyl pyrrolidone as hazardous is 5%, therefore the formulation AGROTAIN® is classified as hazardous on this basis.

3. Manufacture, Importation and Use

The section on manufacture, importation and use is reproduced from the new chemical assessment report (NA/467) (NICNAS, 1997) with new data indicated as (**ND**).

NBPT is not manufactured in Australia.

AGROTAIN® containing NBPT is imported to Australia in 1000 L mini-bulk (**ND**) sealed containers where it is transported to approximately 20 centres for reformulation.

Import volumes of AGROTAIN® are over 22 tonnes (4.24 tonnes NBPT) per year (**ND**).

Nitrogen losses due to ammonia volatilisation occur with urea or urea-based fertilisers, in part, because of rapid hydrolysis of urea on or near the soil surface by free, microbially generated urease. NBPT is a urea fertiliser additive that temporarily retards the enzymatic breakdown of urea by inhibition of urease. This provides an effective means of managing losses of nitrogen in the form of ammonia from surface-applied urea-containing fertilisers.

In Australia, AGROTAIN® is used in combination with granular urea and with urea ammonium nitrate (UAN) liquid fertilisers. NBPT in the product of AGROTAIN® is added to granular urea to give a maximum concentration of 0.064% w/w NBPT, and to UAN at a rate up to 0.038% w/w (**ND**).

4. Occupational Exposure

No new data were provided for assessment of the occupational exposure for the secondary notification of NBPT. The occupational exposure assessment is reproduced from the new chemical assessment report (NICNAS, 1997) and updated to reflect the changes in the Manufacture, Importation and Use section.

NBPT is imported as a 20% constituent of the formulation AGROTAIN®. This is a liquid packaged in 1000 L mini-bulk containers and transported to reformulating facilities for application to granular urea fertilisers. Occupational exposure during transport, unloading and warehousing of AGROTAIN® is limited to accidental release and any subsequent exposure.

Potential occupational exposure to NBPT is greatest during application to the granulated fertiliser and to a lesser extent during fertiliser usage. During the process of application of AGROTAIN® (containing 20% NBPT) to the granulated urea fertiliser, exposure is to a much higher concentration than during usage of the fertiliser which contains only 0.064% w/w of the notified chemical. At the reformulation sites, AGROTAIN® is decanted from the plastic drums into spraying equipment for application to granular urea. Impregnation of urea with the AGROTAIN® concentrate is done prior to bulk blending with any other fertiliser components. After spraying over urea, the fertiliser is tumbled in the spraying equipment, in order to provide a uniform coverage. AGROTAIN® is absorbed into urea granules during mixing.

During spraying, a hood cover is used to catch any product drift, and spray operations are conducted in an enclosed building. Spray operations should be conducted in well ventilated areas. Up to 100 employees spread over 20 sites are involved in the reformulation process. Their exposure is limited by the provision of rubber gloves, long sleeved clothing and eye protection. The main exposure pathways are dermal and ocular although there is also limited potential for inhalational exposure via mists or dusts. Dust is generated during bagging and transferral of treated urea, the low concentration of the notified chemical (0.064%) in this product limits exposure.

Occupational exposure to NBPT may occur during subsequent handling prior to farm use. Fertiliser dealers handle the treated urea however it is packaged in either 50 kg bags, 1 tonne bulk bags, or in bulk. Extensive exposure is very unlikely.

Farmers/applicators transfer the treated fertiliser from farm storage areas to application equipment (spreaders, drills etc.). The fertiliser is either broadcasted or applied to the subsoil. Exposure to NBPT is again limited by the low concentration in the treated fertiliser, but also by the method of application, type of agricultural vehicle and frequency of exposure. The notifier has provided an exposure analysis based on a USEPA model for pesticide exposure (USEPA, 1992). Exposure estimates using this model are of the order of 0.0069 mg/kg/day.

4.1 Conclusion

Occupational exposure to NBPT during reformulation is likely during application to the granulated fertiliser. However, exposure is not likely to be extensive.

Occupational exposure to NBPT during application for farm use is expected to be low.

5. Public Exposure

No new data were provided for assessment of the public exposure for the secondary notification of NBPT. The public exposure assessment is reproduced from the new chemical assessment report (NICNAS, 1997) and updated to reflect the changes in Manufacture, Importation and Use section.

AGROTAIN® in liquid form containing 20% of NBPT is imported and transported to customers for reformulation in enclosed areas at industrial plants. No public exposure occurs during the reformulation process.

Fertilisers containing 0.053%-0.064% (granular urea) and 0.038% (UAN solution) NBPT are available to farmers when applied to topsoil or subsoil by spreaders, drills or other equipment. Public exposure to NBPT is unlikely to occur.

NBPT may be absorbed by crops grown on the treated soil. The company stated that residues in wheat, corn, radish and leaf lettuce were studied (reports not available). Low levels of radioactivity were present in each of the crops at early growth stages or just after application. During plant growth, the levels of radioactivity decreased markedly, by factors of 75%-90%. NBPT per se was not detected in lettuce leaf (< 1 ppb), in which the maximum radioactivity was found. Wheat grain contains less than 2 ppb and wheat straw contains less than 20 ppb of the notified chemical. The estimated application rate is very low, 0.046 kg/ha of NBPT; therefore, residues of NBPT in food commodities are expected to be negligible. Leaching into groundwater from the soil is expected to be low.

In the case of accidental spillage during transport, the public may be exposed to NBPT. However, public exposure will be minimal if the spills are properly contained.

There is no garden use of the product.

5.1 Conclusion

Based on available information, public exposure to NBPT is expected to be low.

6. Environmental Exposure

No new data were provided for assessment of the environmental exposure for the secondary notification of NBPT. This section is reproduced from the new chemical assessment report (NICNAS, 1997) and updated to reflect the changes in Manufacture, Importation and Use section.

6.1 Release

At the reformulation sites, AGROTAIN® is applied to granular urea. Impregnation of urea with the AGROTAIN® concentrate is done prior to bulk blending with any other fertiliser components. During spraying, a hood cover is used to catch any product drift, and spray operations are conducted in an enclosed building.

Subsequent processing indicates that very little of the material remains in the mixing equipment. Any residues that do remain are rinsed off with water, and it is likely this rinsate will enter the sewer.

Residues from drums may be disposed of through washing to sewer. Residues are minimal, with the cost of the material ensuring as little as possible remains in containers. Drums are either sent to secure landfill, or recycled.

After mixing, the end product (containing NBPT at around 0.064% w/w) is transported to farms in either 50 kg bags, 1 tonne bulk bags, or in bulk. Bulk shipment is the main method, increasing exposure in the case of accidental spillage.

During end use, NBPT is applied directly to soil with the application of the fertiliser. The company has clarified this is predominantly as a pre planting application to cereals etc, where the fertiliser is added with the last soil working prior to planting, or in combination with seeding. Either way, the fertiliser is applied under the soil surface. The fertiliser may also be applied as a top or side dressing, eg. to rice crops, where irrigation/rainfall carries it into the soil.

NBPT-treated urea is applied at rates similar to the rate of application of urea recommended for crop production (discussed in Chapter 10 - Environmental Risk Characterisation).

There is no home garden use of this product.

All clean up of spills and disposal of empty packaging are carried out according to the Material Safety Data Sheet (MSDS).

6.2 Fate

NBPT is imported into Australia for incorporation into granular urea and urea ammonium nitrate (UAN) liquid fertilisers. Its function is to retard the enzymatic breakdown of urea by inhibition of urease, thereby slowing the mineralisation of urea to carbon dioxide and ammonia, as nitrogen losses due to ammonia volatilisation occur with urea fertilisers, in part, because of rapid hydrolysis of urea on or near the soil surface by free, microbially generated urease.

The preferred action of the urease inhibitor would be to slow down the hydrolysis process sufficiently to allow the urea fertiliser to be washed into the soil, to increase the amount of nitrogen available to plants. It is necessary for the urea to mineralise, as plants need nitrogen in an inorganic form such as nitrate or ammonium ions. Therefore, urease inhibition cannot last for extended periods of time.

The notified chemical is released to top soil when applied with urea fertilisers. A biodegradation study of this chemical in three soil types was provided, using ^{14}C labelled NBPT. The soil characteristics are presented below:

Characteristic	Soil A	Soil B	Soil C
Soil type	Alfisol	Spodosol	Ultisol
pH	6.5	4.9	8.0
CEC (meq/100g)	10	3	11
Organic Carbon (%)	1.3	0.9	1.2
% Moisture (1/3 bar)	27.2	7.56	15.7
% Sand	45	83.2	66
% Silt	31	12	22
% Clay	24	4.8	12
Soil texture	Loam	Loamy sand	Sandy loam
Bulk density	1.26	1.42	1.31

The three soils were treated with [^{14}C]NBPT at a concentration of 9.5 ppm. This compares with less than 1 ppm in the top 5 cm of soil at recommended application rates (see Chapter 10). The soils were then maintained in biometer flasks at about 22°C in darkness. The study was halted after 50% of the applied NBPT was mineralised.

Mineralisation was rapid in all three soils. In soils A and B, 53%-55% of the applied dose was converted to $^{14}CO_2$ after 8 days. In soil C, 52% of the applied dose was mineralised after 16 days.

From these results, it can be stated that mineralisation of NBPT is a significant route of dissipation in soils.

For all three soils, the bound soil ^{14}C-residues accounted for around 40% of the applied dose. This adsorbed material could be either the parent compound or metabolites of NBPT. The test did demonstrate that bound residues of NBPT were formed in soil.

6.3 Conclusion

Environmental exposure to NBPT arising from reformulation and end use activities is expected to be low.

7. Human Health Hazard Assessment

This section contains a short summary of the data relevant to the human health hazard assessment of the chemical. Robust summaries of the data available for the assessment of NBPT as a new chemical are reproduced from the new chemical report in Appendix I of this report without modification.

Detailed descriptions of the new data submitted for the secondary notification are included in this section.

7.1 Toxicokinetics and metabolism

Metabolism of NBPT in rats (ND)

A study on the metabolism of NBPT in rats including some toxicokinetic data was available for assessment (Ricerca, 1997). The study conducted in a GLP laboratory with QA was designed to generate pharmacokinetic data and identify metabolites of NBPT.

A pilot study was initially carried out in two dosed males and one control male rat with a sampling time of 48 hours to determine whether the radiolabelled NBPT is expired in air. In the main study, a single oral dose of ^{14}C-NBPT was administered by gavage to eight male Sprague-Dawley rats at an average of 252 mg/kg (206 μCi/kg). This dose level was selected because 250 mg/kg bw/d NBPT had been reported from another study to be the NOEL for cholinesterase depression effect. One rat receiving the vehicle only was used as the control. Samples of expired air, urine, faeces, cage rinses and blood were collected and analysed for radiolabelled contents. Samplings were terminated at 168 hours after dosing in the main study. The liver, mesenteric fat, kidney, spleen, blood and residual carcass were collected for analysis. Metabolites of NBPT were characterised and identified from urine samples. Samples from the two controls (pilot study and the main study) were analysed as the background.

The pilot experiment in two males showed a total recovery of 86.43% with the major amount (40.22% of the administered dose) in expired air 48 hours after dosing. Similar results occurred in the main study with a total recovery rate of 83.04%.

Absorption of NBPT via oral route was almost complete, as 74.39% of the given dose was considered to be absorbed. Four out of 8 rats had blood sample collected through a jugular cannula at various times after dosing (between 1 to 120 hours). Times at which peak concentrations were reached in the blood stream (t_{max}) in three of the four rats were within one hour of administration with a mean peak concentration (C_{max}) of 80.18 μg-equi/g. No data were available on dermal or inhalation absorptions.

NBPT was distributed to most of the organs based on the data at termination. Samples from liver, mesenteric fat, kidney, carcass and spleen combined registered higher NBPT concentrations than that in blood samples. Although lung samples were not measured in the experiment, NBPT is believed to be distributed to the lungs before its elimination into air. Regarding the quantitative distributions in

different organs, higher amounts of NBPT were seen in the carcass, liver and blood with minor amounts in the kidney, spleen and mesenteric fat. After 7 days, 2.92% of the given dose remained in the body. NBPT concentrations in blood samples followed a biphasic declination pattern, decreasing rapidly to less than 14% of the C_{max} 24 hours after dosing and then to <5% by 168 hours. There were no data on protein binding or enterohepatic circulation of NBPT.

Two major metabolites of NBPT were separated and identified from the urine samples. One was the glucuronic acid conjugate of NBPT, the structure of which was confirmed by LC/MS. Another was confirmed to be N-(n-butyl)-thiophosphoric diamide by both LC/MS and NMR. No metabolic pathways had been investigated on the formation of CO_2 which was excreted via lungs.

Elimination of NBPT from the blood stream showed a linear declination with a calculated t½ of 78 hours. After a single oral dose, 80.12% NBPT was excreted in 7 days. NBPT was mainly eliminated via expired air (as CO_2), urine and faeces with averages of 35.4%, 24.4% and 8.7% of the administered dose, respectively. Some residues were recovered from cage rinses (11.7%).

7.2 Effects on laboratory animals and other systems

7.2.1 Acute toxicity

Four acute oral toxicity studies of NBPT in rats were assessed in the NA/467 report. The oral LD50 was 1000-4000 mg/kg using propylene glycol as vehicle, and greater than 2000 mg/kg when using distilled water or olive oil as vehicle. Three acute dermal toxicity studies in rabbits were assessed in the NA/467 report. The dermal LD50 for NBPT was greater than 2000 mg/kg. NBPT is of low acute oral and dermal toxicity.

No acute inhalation toxicity data were submitted.

7.2.2 Irritation and sensitisation

The NA/467 report assessed a skin irritation study of NBPT. Of the six rabbits tested, only one animal had mild erythema at 24 hours which was reversible by 48 hours. A skin sensitisation study of NBPT using guinea-pigs found that NBPT was not a skin sensitiser.

Primary eye irritation of NBPT (ND)

An acute eye irritation study of NBPT was conducted according to OECD TG 405 (Safepharm Laboratories, 2001c). There were no reported significant protocol deviations.

A volume of 0.1 mL of NBPT (white powder) weighing approximately 80 mg was placed into the conjunctival sac of the non-irrigated right eye of a New Zealand White rabbit. Observations were made at: 1, 24, 48 and 72 hours, and 7, 14 and 21 days.

The single application produced irreversible effects in the rabbit eye. Reactions noted included translucent corneal opacity, iridial inflammation, moderate conjunctival irritation, dulling of the normal lustre of the cornea, ectropion and vascularisation with a generalised ingrowth of vessels for approximately 3–4 mm.

At the 21-day observation period, scattered or diffused corneal opacity, and vascularisation were noted in the treated eye. The scores for ocular irritation are presented below:

	Score at Different Times after Treatment						
	1 hr	**24 hrs**	**48 hrs**	**72 hrs**	**7 days**	**14 days**	**21 days**
Cornea							
Opacity	0(D)	1	2	2	2(V)	2(V)	1(V)
Area	4	4	4	4	4	1	1
Iris	1	1	1	1	1	0	0
Conjunctivae							
Redness	2	2	2	2	2	2(Ec)	0
Chemosis	2	2	2	2	2	1	0
Discharge	3	2	2	2	2	1	0

D = dulling of the normal lustre of the cornea; V = vascularisation, generalised ingrowth of vessels for approximately 3-4 mm; Ec = ectropion

The OECD TG 405 states that 'if the results of this test indicate the substance to be corrosive or a severe irritant to the eye using the procedure described, further testing for ocular irritancy should not be performed'. Thus, no further ocular irritancy test was performed in that laboratory.

NBPT was found to cause severe damage to the rabbit eye due to ocular lesions being present at the end of the observation time.

7.2.3 Repeated dose study

Fifteen-day repeated dose study

The NA/467 report assessed a 15-day repeated dose study of NBPT (test method was not specified and duration did not conform to OECD guidelines) [Hazleton Laboratories, 1990a]. The study was a dose range-finding study, where NBPT was administered to SD rats (5/sex) at 0, 250, 500, 1000 and 2000 mg/kg bw/d by gavage for 15 days.

No death occurred during the treatment phase of the study. At the top two dose levels, animals exhibited salivation and languid behaviour. Clinical chemistry results showed significant decrease in blood urea nitrogen (BUN) in all dosed animals except the lowest dose males, significantly decreased total cholesterol in the highest dose groups, and significantly decreased triglycerides in highest dose males. An increase of alanine aminotransferase (ALT) was seen in the two mid-dose male groups. At necropsy, liver weights were not affected by the treatment, but the absolute and relative spleen weights were reduced in the highest dose animals.

The study included an assay on cholinesterase activities. Plasma, erythrocyte and brain samples for individual animals were collected within the range of 2 to 5 hours after dosing, and their cholinesterase activities were determined by an AutoAnalyzer. Inhibition of cholinesterase activity by NBPT was calculated using the following equation:

$$Mean\ inhibition\ \ (\%) = \frac{Control\ mean - Test\ mean}{Control\ mean} \times 100\%$$

The assay showed that the cholinesterase activities of erythrocyte and brain were significantly inhibited by NBPT in a dose-dependent manner. However, the plasma cholinesterase (pseudocholinesterase) levels were not affected in the study. The percentages of inhibition of cholinesterase activity at week 3 are presented below:

Dose level (mg/kg bw/d)	Plasma cholinesterase		Erythrocyte cholinesterase		Brain cholinesterase	
	male	female	male	female	male	female
250	6	36	11	16	6	5
500	-6	29	28*	20*	11	10
1000	0	36	34*	36*	21*	20*
2000	6	33	55*	64*	27*	27*

* $P \leq 0.05$

A NOAEL of 250 mg/kg bw/d was established from the study based on a significant decrease of cholinesterase activity at 500 mg/kg bw/d.

Ninety-day repeated dose study (ND)

A 90-day dietary study in rats incorporating a neurotoxicity screen was carried out in accordance with US EPA guidelines (Huntingdon Life Sciences, 1997).

NBPT (0, 200, 1000 and 5000 ppm) was administered to Crl:CD BR rats in their diet for 90 days. Each dose group consisted of 10/sex as the main group and 5/sex as the satellite group. The overall mean intakes of NBPT were 0, 15, 74 and 377 mg/kg bw/d for males and 0, 17, 88 and 445 mg/kg bw/d for females corresponding to 0, 200, 1000 and 5000 ppm, respectively. During the pre-dose period and weeks 4, 8 and 13, half of the animals from the main groups and all satellite animals were screened for neurotoxicity. At week 14, the satellite animals were killed for histopathological examinations of the nervous system and the main group animals were sacrificed for post mortem examinations.

High-dose males had significantly lower cumulative food consumption during weeks 1 to 12. Efficiency of food utilisation was impaired for the first 3 weeks in both males and females at high-dose level, and the cumulative body weight gain of these animals was significantly lower than controls during weeks 1-4.

Haematological results showed high-dose males had significantly lower white blood cell counts accompanied with decreased lymphocyte counts at week 5, and high-dose females had significantly increased platelet counts at weeks 5 and 13. Biochemistry results showed that high-dose animals had lower levels of ALT, AST, AP and phosphorus; mid-dose animals had lower levels of AST, AP and phosphorus; and low-dose animals had lower phosphorus levels. Due to a wide range of phosphorus values in the control group, levels of phosphorus in mid- and low-dose animals are considered to be within background levels. Similar to studies with other organic phosphate compounds, animals after treatment with NBPT had lower concentration levels of liver enzymes such as ALT, AST and AP in blood

samples. These changes seem to be related to the organic phosphate compound treatment and the toxicological significance of these changes is not known.

At necropsy, the high-dose males had significantly higher relative liver weights ($p<0.01$) with significantly increased incidence of minimal centrilobular hepatocyte hypertrophy (60% vs 0% in the controls, $p<0.01$). Hepatocyte hypertrophy was also seen in the mid-dose males, but the incidence was within the limits of historical background reported in this age and strain of rats in the testing laboratory. Minimal centrilobular hepatocyte hypertrophy was seen in some control and treated female rats but was not considered to be treatment-related.

Incidence of foci of mineralisation in the kidney in the control, low-, mid- and high-dose female groups were 2/9, 2/10, 2/10 and 6/10, respectively. The high-dose females also had more severe cases of mineralisation in the kidneys. However, the findings did not attain statistical significance in any groups. Foci of mineralisation in the kidney among female rats are sex-related spontaneous findings and considered to be related to circulating oestrogen levels. The slight high incidence of mineralisation in the kidneys of high-dose females may reflect an altered hormonal balance.

Significantly increased uterus weights were seen in the mid-dose ($p<0.05$) and high-dose ($p<0.01$) females. Incidences of fluid distension during macroscopic examination in the control, low-, mid- and high-dose groups were 0/9, 3/10, 5/10 and 6/10, respectively. Microscopic pathological examinations showed that incidences of luminal dilatation in the uterus in the control, low-, mid- and high-dose groups were 0/9, 3/3, 5/5 and 6/10, respectively. Both fluid distension and luminal dilatation are normal physiological events associated with oestrus cycles. The toxicological significance of their occurrence in NBPT-treated animals is unknown. Without historical animal data from the testing laboratory, increased incidences of fluid distension and luminal dilatation of the uterus are considered to be treatment related in female groups.

Neurotoxicity screening showed transitory changes in behaviour characterised by decreased grip strength in high-dose males and females, and a low incidence of hunch posture in high-dose females during week 4 examinations. There were no significant differences in neurobehavioural tests between the NBPT-treated animals and the controls in the subsequent two examinations. For the satellite animals, neuropathology provided no evidence of neurotoxicity.

A NOAEL of 74 mg/kg bw/d for males is established from the 90-day study based on liver effects and changes in neurobehaviour and haematology and the LOAEL is considered to be 377 mg/kg bw/d. A NOAEL could not be determined in females in the study, but the LOAEL for females is 17 mg/kg bw/d based on effects seen in the uterus.

7.2.4 Genotoxicity

NBPT showed little evidence of mutagenicity in two Ames tests with and without metabolic activation. An in vivo mouse micronucleus study was negative for evidence of clastogenicity.

7.2.5 Reproductive and developmental toxicity (ND)

Prenatal developmental toxicity study in rats

A prenatal developmental toxicity study of NBPT in rats was conducted according to OECD TG 414 (Huntingdon Research Centre, 1995a).

Pathogen-free female Crl: CD®BR VAF/Plus rats (8-10 weeks old) were time-mated to identified males of the same strain. Four groups (25 females each) were treated with 0 (control), 30, 125 and 500 mg/kg bw/d NBPT in aqueous polyethylene glycol 300. NBPT was administered by gavage on day 6 of pregnancy (GD 6) and continued daily up to and including day 15 of pregnancy (GD 15). On day 20 of pregnancy, all the females were sacrificed for post mortem examination, litter values were determined and foetuses were subsequently examined for any visceral or skeletal changes.

All high-dose females (100%) displayed post-dosing salivation and associated wet coats during the treatment period. Post-dosing salivation was first observed on the second day of dosing. The number of rats affected on any particular day varied and was generally higher during the last four days of treatment. Five high-dose animals showed noisy respiration on isolated occasions between GD 11-15. Eight out of 25 animals in the mid-dose group showed post-dosing salivation on isolated occasions during the last three days of treatment and one animal showed noisy respiration on GD 13. One low-dose animal showed noisy respiration on GD 12. Both salivation and noisy respiration are considered to be treatment-related since these symptoms were not seen in the controls.

Bodyweight gain in high-dose females was significantly lower than the controls associated with lower food consumption in GD 6-7. Water consumption in high-dose animals during GD 8-15 was significantly higher. Other observations were found to be comparable to the controls. At necropsy, low incidence of occasional macroscopic changes at autopsy did not indicate any obvious adverse effect of treatment.

The litter data showed no obvious adverse effects of treatment on the implantation rates, live litter size, sex ratio, litter weight, mean foetal weight or gravid uterine weight. The foetuses showed no obvious effects of treatment on the number or distribution of foetuses with either visceral or skeletal abnormalities, or skeletal variants. The high-dose females had significantly high incidences of early in utero deaths ($p \leq 0.05$) and total in utero deaths ($p \leq 0.01$) than in the control group. However, since there was no dose response in the number of litters affected (control: 10/25, low-dose: 11/25, mid-dose: 11/25 and high-dose: 14/25) and the maximum number of dead embryos did not exceed 3 regardless of litter size, the differences were considered unrelated to treatment.

A NOAEL for maternal toxicity in this study is 125 mg/kg bw/d based on decreased bodyweight gain in high-dose females and clinical symptoms such as post-dosing salivation and noisy respiration seen at the LOAEL of 500 mg/kg bw/d. The NOAEL for developmental toxicity is 500 mg/kg bw/d, the highest dose tested, as no developmental effects were reported at this dose.

Prenatal developmental toxicity study in rabbits (ND)

A prenatal developmental toxicity study of NBPT in rabbits was conducted according to the OECD TG 414 (Huntingdon Research Centre, 1995b).

Four groups of female New Zealand White rabbits (20 animals per group), which had completed coitus and had been injected intravenously with luteinising hormone, were treated with 0 (control), 12.5, 50 and 200 mg/kg bw/d NBPT in aqueous polyethylene glycol 300. NBPT was administered once daily by gavage from day 6 to day 18 post coitum inclusive (GD 6-18). On day 29 of pregnancy, the females were sacrificed for post mortem examination, litter values were determined and foetuses were subsequently examined for any visceral or skeletal changes.

There were two mortalities on the study. One low-dose female was unable to move her hind limbs and sacrificed on GD 1 for humane reasons. Necropsy revealed a fracture of the spinal cord in the lumbar region. One high-dose female was sacrificed on GD 12 due to poor conditions. The animal had shown lack of appetite (inappetence). Necropsy examination showed a distended gall bladder with a few pale foci and a few olive-green diffuse subcapsular areas adjacent to the gall bladder in the liver. Both deaths were not considered to be treatment related.

There were no obvious clinical signs following NBPT treatment or changes in bodyweight gain or food consumption. Macroscopic post mortem examination showed that incidences of subcapsular scarring of kidneys in the control, low-, mid- and high-dose groups were 2/20, 4/20, 4/20 and 7/19, respectively. The rate in the high-dose group was significantly higher than that in the controls ($p<0.05$).

One low-dose and one mid-dose female aborted their entire litters for unknown reasons on GD 18–20 and GD 24-26, respectively. The study report indicated that the incidences were coincidental and unrelated to the treatment as there were no instances of abortion observed in the high-dose group. With the exception of two abortions, there were no obvious adverse effects of NBPT treatment on any other litter parameters recorded or foetal morphological abnormalities.

The NOAEL for maternal toxicity is 50 mg/kg/day based on the higher incidence of subcapsular scarring in kidneys as compared to controls at the LOAEL of 200 mg/kg bw/d. The NOAEL for developmental toxicity is 200 mg/kg bw/d, the highest dose in the study based on no adverse effects observed.

Two-generation reproductive toxicity study (ND)

A two-generation reproductive toxicity study in rats was performed in compliance with GLP and in accordance with the OECD TG 416 (Huntingdon Life Sciences, 1999).

Four groups (32/sex) of CD strain (of Sprague-Dawley origin) rats were fed NBPT via dietary administration at concentrations of 0, 200, 800 or 3200 ppm. Treatment of F0 males and females commenced 10 weeks prior to pairing. For F1 males and females, offspring not selected for continuation of the study were sacrificed on day 35 (PND 35). Treatment of selected F1 animals (32/sex) commenced at PND 28, then 10 weeks from weaning prior to pairing until termination (when litters were weaned). After 10-week pre-mating treatment, 1 male and 1 female from the same treatment group were paired in a cage for up to 3 oestrus periods or up to 2 weeks without partner exchange and no pairing of siblings.

The actual amount of NBPT intake varied at different stages (pre-mating, gestation and lactation) of the experiment. The mean intakes in the F0 generation were 334, 84 and 21 mg/kg bw/d. NBPT mean intakes for the F1 generation were 362, 90 and 23 mg/kg bw/d.

For F0 and F1 animals, observations for abnormal signs of toxicity were performed regularly. Organ weight and body weight measurements were conducted in adults and offspring. Adults in the high dose and control groups were subjected to detailed necropsy. Reproductive parameters such as oestrus cycle, mating performance, gestation length and reproductive organ histopathology were investigated. Sperm counts, motility and morphology were determined. The epididymis was examined in mid- and low-dose animals. Offspring were examined for live litter size, viability and timing of developmental milestones such as pinna detachment, hair growth, tooth eruption and eye opening. Sexual maturation was also evaluated.

Systemic toxicity

There were no treatment-related mortalities seen in both F0 and F1 generations. Mortalities in the control, low- and mid-dose groups of the F0 animals were 1, 2 and 1, respectively. All were due to poor clinical conditions. For F1 animals, five mid-dose females were sacrificed for animal welfare reasons.

Significant reductions of bodyweight gain were seen in both high-dose F0 males (10%) and F0 females (17%), and in mid-dose F0 females (12%). At necropsy of adult animals, the relative liver weight was higher in high-dose F0 animals, the absolute kidney weight was lower in F0 high-dose males and the absolute adrenal and spleen weights were lower in F0 high-dose females. Bodyweight gain was significantly reduced in F1 high-dose males between weeks 1-18 (17%) and females between weeks 4-10 (10%). The terminal body weights of those two groups were also significantly lower than the controls. Organ changes in adult animals were seen at necropsy.

Changes in bodyweight gains and organ weights in high-dose F0, F1 and F2 animals

	F0	F1	F2
Males	↓ bodyweight gain, kidney (abs) ↑ liver (rel)	↓ bodyweight gain, kidney (abs), liver (rel) ↑ adrenal (rel), brain (rel)	↓ bodyweight gain, spleen (abs), thymus (abs)
Females	↓ bodyweight gain, adrenal (abs), spleen (abs) ↑ liver (rel)	↓ bodyweight gain, adrenal (abs, rel), kidney (abs, rel), spleen (abs)	↓ bodyweight gain, spleen (abs), thymus (abs)

abs = absolute; rel = relative

At necropsy of offspring at PND 35, both F1 and F2 animals at high-dose had significantly lower body weight and absolute thymus weight. Mid-dose F2 males also had lower absolute thymus weight. However no significant differences were seen for the thymus-to-bodyweight ratios.

Fertility

Treatment of NBPT neither affected the mating performance in F0 animals nor produced adverse reproductive effects in F0 females. The high-dose F0 males had higher relative epididymis weight. Histopathological examination of the epididymis showed that all high-dose F0 males had epithelial fatty vacuolation in the corpus. Other changes also included epididymal fat granulomas, reduced sperm content, luminal germ cells and corpus interstitial inflammatory infiltrate. Sperm evaluation revealed that the percentage of normal morphology, progressively motile, straight line velocity and curvilinear velocity were significantly lower ($p<0.01$) in the epididymis of the high-dose males.

Examination of male reproductive organs revealed that F1 high-dose males had significantly lower seminal vesicle absolute weight, and higher epididymis and testis relative weights. Sperm evaluation from epididymis samples showed that percentage of motile sperm was significantly lower ($p<0.01$) in F1 mid- and high-dose males. Percentage of progressively motile sperm ($p<0.05$) and percentage of rapid sperm ($p<0.01$) were significantly lower at high-dose level. From histopathological results, the epithelial cells lining the epididymal duct exhibited macro and microvesiculation resembling fat vacuoles in all high-dose males and in 13 out of 31 mid-dose males, compared to nil in both the controls and the low-dose group.

For the F1 females, high-dose females had significantly lower ovarian and oviduct weight ($p<0.05$). Histopathological investigations showed that at high-dose level there was a clear increase in the number of animals exhibiting atrophic and mucified vaginal epithelium and histological indications of anoestrus (animals had not yet returned to normal oestrus cycle).

There were no other significant differences between NBPT-treated animals and the controls in reproductive performance.

Development

Mean implantation count and total and live litter size on day 1 of age in high-dose F1 were both slightly lower than in controls, the difference attained statistical significance for live litter size. Other litter parameters were not affected by treatment. Bodyweight of male and female offspring on PND 1 and PND 14 were also not adversely affected but decreased thereafter compared to controls (10%, 7% and 5% for high-, mid- and low-dose males and 12%, 7% and 5% for high-, mid- and low-dose females at PND 14-35). There was no effect on the timing of developmental milestones.

Mean implantation count and total and live litter size on PND 1 were slightly lower at high-dose than in controls (with no effect at mid- and low-dose) in F2. Bodyweight and bodyweight gains for both male and female offspring on PND 14 were also not adversely affected. Thereafter, high-dose male and female offspring had lower weight gain than controls (10% and 7% respectively) at PND 14-35 although a dose response was not seen. There was no effect on the timing of developmental milestones.

No observed adverse effect levels (NOAELs)

The NOAEL for systemic toxicity was determined to be 200 ppm (21 mg/kg bw/d) for females based on decreased bodyweight gain at 800 ppm and above in F0

females. The NOAEL for males is 800 ppm (84 mg/kg bw/d) based on decreased bodyweight gain in F0 and F1 males at 3200 ppm.

Adverse effects on reproductive organs were observed in both male and female rats. These adverse effects could affect fertility. The NOAEL for effects on fertility in males was established as 200 ppm (21 mg/kg bw/d) based on decreased sperm motility and epididymal lesions in F1 at 800 ppm and above. The NOAEL for effects on fertility in females was established as 800 ppm (84 mg/kg bw/d) based on delayed or non-recovery of oestrus cyclicity post-pregnancy for F1 at 3200 ppm.

The NOAEL for developmental toxicity was not determined. The decreased bodyweight gain in pups was considered to be due to systemic toxicity. NBPT is not considered to be toxic to development.

7.3 Effects observed in humans (ND)

An allegation/incident report submitted to the US EPA under TSCA in 2006 was provided for secondary notification.

In November 2006, two workers became ill after handling AGROTAIN®. The alleged symptoms were nausea and nose bleed which occurred after work was complete. One of the workers sought medical attention from his physician. Subsequent investigation found that the two workers, wearing respirators with recommended cartridges, performed installation and calibration of an AGROTAIN®-urea spray application system in a confined space with no mechanical exhaust. They reported that, after several hours of work, they could smell the product despite wearing respirator protection. They continued working and utilised the same cartridges throughout the 2½ days.

The ensuing investigation revealed that the respirators failed to perform during the course of installation and calibration work. The most likely cause for the respirator failure was saturated cartridges. The company stated that employees are not exposed to the aerosol spray under normal application conditions and no production workers have reported symptoms. The company amended current product label to read “Apply product with coarse spray only. Do not atomize”.

7.4 Regulatory classification based on hazard

In Australia, determination of whether a substance is hazardous to health of workers is based on the *Approved criteria for classifying hazardous substances* (NOHSC, 2004), which covers physicochemical properties, toxicological and ecotoxicological effects.

The classification for health effects is based on experimental studies. The hazard classifications based on the overall data including new data provided for secondary classification are presented below.

7.4.1 Physicochemical hazards

Based on the known physicochemical properties, NBPT is not considered to be dangerous due to its physicochemical properties.

7.4.2 Health hazards for NBPT

Assessment and classification as a new chemical

From the new chemical assessment report (NICNAS, 1997), NBPT was shown to have low acute oral and dermal toxicity in rats. NBPT has a potential for skin irritation in a study using rabbits where minor effects were evident but reversible and did not meet the Approved Criteria for skin irritation. The classification of the formulation AGROTAIN® as hazardous (irritant) is discussed below.

NBPT was classified as an eye irritant following the new chemical assessment. The chemical was considered to be of low acute toxicity, not a skin sensitiser and not genotoxic.

Assessment and classification of AGROTAIN® as a new chemical

AGROTAIN® is of low acute oral toxicity with a LD50 greater than 5000 mg/kg in rats. Clinical signs of the 10 tested animals included red-stained face, thin appearance, possible bronchial congestion, hypoactivity, staggered gait, dyspnea, prostration, and/or absence of grasping reflex (Corning Hazleton, 1996a).

AGROTAIN® is of low acute dermal toxicity with a LD50 greater than 2000 mg/kg in rabbits. In the study, all 10 tested animals had slight erythema, and one rabbit had a slight oedema reaction (Corning Hazleton 1996b).

The primary dermal irritation potential of AGROTAIN® was evaluated in 6 rabbits under 4-hour semi-occluded conditions. AGROTAIN® produced slight erythema reactions in 5 animals and a slight oedema reaction in one animal. All irritation cleared by the 96-hour observation. The average of individual index scores was 0.7 (Corning Hazleton 1996c).

Data on eye irritation potential was available for the imported commercial formulation AGROTAIN®. In a rabbit study, significant irritating effects were seen on conjunctiva, cornea and iris (Corning Hazleton, 1996d).

Based on the data provided AGROTAIN® meets the Approved Criteria as an eye irritant.

7.4.3 Classification based on assessment of new data

Acute eye irritation

An acute eye irritation study of NBPT produced irreversible effects. Corneal opacity score at 48 hours to day 14 was 2. Iris lesion score was 1 from hour 1 to day 7. A score of 2 was observed from hour 1 to day 7 for conjunctivae chemosis. At the 21-day observation period, scattered or diffused corneal opacity, and vascularisation were noted in the treated eye.

Classification: Based on the rabbit data, NBPT meets the *Approved criteria for classifying hazardous substances* (NOHSC, 2004) for classification as an irritant and the risk phrase R41 (Risk of serious damage to eyes) is applicable.

Repeated dose toxicity

Repeated dose experiments in animals at high doses showed changes in animal body weights and bodyweight gains from clinical observations, changes in liver and kidney weights with histopathological evidences at necropsies, and changes in biochemical assays. In addition, salivation and languid behaviours and lower grip strength were observed at high doses. When combining all repeated dose studies for NBPT (including a repeat dose study with a duration of 15 days from the new assessment report showing decreased erythrocyte cholinesterase levels in two high dose groups), the NOAEL for males is 74 mg/kg bw/d based on liver effects and changes in neurobehaviour and haematology and the LOAEL is considered to be 377 mg/kg bw/d. A NOAEL could not be determined in females in the study, but the LOAEL for females is 17 mg/kg bw/d based on effects seen in the uterus.

Based on the repeated dose toxicity studies provided for secondary notification, NBPT does not meet the *Approved criteria for classifying hazardous substances* (NOHSC, 2004) for classification as hazardous for repeated dose or sub chronic toxicity.

Reproductive toxicity

For reproductive toxicity, the two-generation study provided well conducted data for NBPT. The chemical caused changes in reproductive organs with histopathological findings in both males and females, and abnormalities in sperm evaluations. The NOAEL in males is 21 mg/kg bw/d based on decreased sperm motility with epididymal lesions at 84 mg/kg bw/d, and the NOAEL in females is 17 mg/kg bw/d based on the increase of uterus weight at 88 mg/kg bw/d (from the 90-day repeat-dose study). An overall NOAEL is considered to be 17 mg/kg bw/d for reproductive toxicity of NBPT.

Classification: Based on available animal data, NBPT meets the *Approved criteria for classifying hazardous substances* (NOHSC, 2004) for classification as a Category 3 reproductive toxicant and the risk phrase R62 (Possible risk of impaired fertility) is applicable.

Developmental toxicity

In reproductive studies in rats and rabbits, no developmental effects were observed at doses of 500 and 200 mg/kg bw/d, respectively following administration of NBPT by gavage.

In addition, in an oral 2-generation study in rats, there was no dose-response effect on developmental milestones for F1 and F2 generations. Reduced bodyweight gain was observed at the highest dose (362 mg/kg bw/d) at which maternal toxicity was also reported. The NOAEL for developmental toxicity was not determined. The decreased bodyweight gain in pups was considered to be due to systemic toxicity.

Based on available animal data provided for secondary notification, NBPT does not meet the *Approved criteria for classifying hazardous substances* (NOHSC, 2004) for classification a developmental toxicant.

7.4.4 Classification under the Globally Harmonised System (GHS)

The hazard classification of NBPT using the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) published by the United Nations is presented below. This system is not mandated yet in Australia and carries no legal status, but is presented for information purposes. GHS classification and information documentation is available at

http://www.unece.org/trans/danger/publi/ghs/ghs_rev01/01files_e.html.

GHS classification for health hazards of NBPT:

Hazard category	***Signal word***	***Hazard statement***	***Concentration cut-offs for products/mixtures***
Eye irritation: Category 1 Serious eye damage	Danger	Causes serious eye damage	Cat. 1 = Conc. ≥ 3.0% Cat. 2 = Conc. ≥ 1.0% but < 3.0%
Toxic to reproduction: **Category 2**	Warning	Suspected of damaging fertility or the unborn child	Conc. ≥ 0.1%[1] Conc. ≥ 3.0%[2]

[1] If a category 2 reproductive toxicant is present in the mixture as an ingredient at a concentration between 0.1% and 3.0% every regulatory authority would require more information on the SDS for a product. However a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 3.0%, whereas others would normally not require a label in this case.

[2] If a category 2 reproductive toxicant is present in the mixture as an ingredient at a concentration ≥3.0%, both an SDS and a label would generally be expected.

8. Environmental Hazard Assessment

The environmental hazard assessment is reproduced from the new chemical assessment report (NICNAS, 1997).

The following ecotoxicity studies have been supplied by the notifier. The tests were carried out according to OECD Test Methods.

Ecotoxicity test results

Test	Species	Results (mg/L)
Acute Toxicity (S; N)	Bluegill (*Lepomis macrochirus*)	96 h LC50=1140
Immobilisation (S; N)	Water Flea (*Daphnia magna*)	48 h EC50=290
Growth Inhibition (S; N)	Algae (*Selenastrum capricornutum*)	96 h EC50=280

S=Static; N=Nominal Concentration

At all concentrations tested, (700, 1100, 1800, 3000 and 5000 ppm) sub-lethal or lethal effects to fish were observed. At 700 and 1100 ppm, the noted effects were largely lethargy, while in higher concentrations, effects were primarily lethal (Resource Analysts, 1990a).

Two end points, immobilisation and death were used during daphnia testing. Using probit analysis, the 48 hour LC50 equals 350 ppm, while the 48 hour EC50 (immobilisation) of 290 ppm was obtained using nonlinear interpolation (Resource Analysts, 1990b).

Using probit analysis, the values of EC10 = 110 ppm, EC50 = 280 ppm and EC90 = 760 ppm were obtained for algae. These data relate to growth rate, with results determined by cell count (Resource Analysts, 1990c).

While no specific tests had been conducted on earthworms, the company stated that no reports of any adverse effects on earthworms had been reported during widespread field trials with the notified product.

Similarly, no definitive avian toxicity studies had been conducted. The notifier has provided some figures from a recent pilot metabolism study in which a 250 mg/kg bodyweight of carbon-14 labelled NBPT was administered to laying hens. The results of this indicated an LD50 of greater than 50 mg/kg bodyweight in hens.

8.1 Conclusion

NBPT is practically non-toxic to bluegill (*Lepomis macrochirus*), water flea (*Daphnia magna*) and algae (*Selenastrum capricornutum*).

8.1.1 Classification under the Globally Harmonised System (GHS)

Using the GHS classification system, NBPT is not classified for acute aquatic toxicity.

9. Human Health Risk Characterisation

9.1 Critical health effects

The critical health effects for NBPT are eye irritation and adverse reproductive effects.

NBPT is found to produce serious eye damage in rabbits. Studies on AGROTAIN® also reported eye irritation.

NBPT has low acute toxicity by dermal or oral route. The chemical has some potential for skin irritation where minor effects were evident in a rabbit study. A skin sensitisation study using guinea-pigs found that NBPT was not a skin sensitiser. NBPT showed little evidence of mutagenicity and was also negative for evidence of clastogenicity.

NBPT is found to produce adverse effects on reproductive organs in rats with histopathological findings in both males and females, and abnormalities in sperm evaluations. An overall NOAEL is 17 mg/kg bw/d for fertility effects of NBPT.

9.2 Occupational health risk estimation

AGROTAIN®, containing 20% NBPT and formulated prior to importation into Australia, is packaged in 1000 L mini-bulk sealed containers. It is transported to approximately 20 centres in Australia for reformulation. Worker exposure during transport is unlikely except in the event of a spill. The MSDS for AGROTAIN® provide instructions for clean-up following a spill. In the event of a spill during transport to the reformulation sites or within the reformulation sites, a risk of serious eye damage from accidental splashing may occur.

Exposure to NBPT in AGROTAIN® may also occur during loading/unloading and warehousing of AGROTAIN® and is limited to accidental release. Skin and eye contact with 20% NBPT may occur.

The highest potential for occupational exposure is likely to be during reformulation. Imported AGROTAIN® containing 20% NBPT is applied to granular urea fertiliser. Reformulators manually handle AGROTAIN®. The product is decanted from plastic drums into spraying equipment for application to granular urea. During spraying, a hood cover is used to catch any product drift, and spray operations are conducted in an enclosed building. Exposure is limited by enclosed reformulating equipment, clothing and personnel protective equipment. Dermal exposure is the main route of exposure for reformulators. There is also a risk of serious eye damage if splashing of NBPT occurs during manual handling by reformulators. NBPT causes serious damage to eyes at a concentration equal to of greater than 10%. Risk of adverse systemic toxicity is considered to be low. NBPT adversely affects reproductive organs in rats and there is a potential risk of effects on fertility with prolonged exposure to preparations containing $\geq 5\%$.

Exposure to NBPT may also occur during subsequent handling of the fertiliser preparations (containing 0.038%-0.064% NBPT) prior to farm use. Fertiliser dealers handle the NBPT-treated urea which are packaged in either 50 kg bags, 1 tonne bulk bags, or in bulk and extensive exposure is very unlikely.

Exposure during application by agricultural workers is minimal since the final fertiliser preparations contain 0.038%-0.064% NBPT. At this range, NBPT does not cause severe damage to the eyes, based on a cut-off concentration for NBPT of 10%. At this low concentration of NBPT the risk of serious damage to the eyes to the workers handling the fertiliser preparation is considered to be low.

The estimated dermal exposure for applictors as provided by the new chemical assessment report is 0.0069 mg/kg/day. Using the NOAEL of 21 mg/kg bw/d derived from fertility effects, the calculated margin of exposure (MOE) for NBPT during fertiliser application is 2464. The calculated MOE indicates that fertility health risk for applicators of the fertiliser application is low.

9.3 Public health risk estimation

Urea fertilisers containing NBPT are used by farmers. Although NBPT is an organic phosphate and causes serious damage to eyes in rabbits, the low level (0.038%-0.064%) present in fertiliser formulations is not expected to lead to a significant hazard. Residues of the notified chemical in food commodities are expected to be negligible. There is no home garden use of the product.

9.4 Conclusion

Risk characterisation shows concerns for eye irritation and reproductive effects in reformulators manually handling NBPT. However, health risk for applicators and the public is expected to be low.

10. Environmental Risk Characterisation

This section is reproduced from the new chemical assessment report (NICNAS, 1997) and updated to reflect the changes in Manufacture, Importation and Use section. The calculations based on the import volume of 150 tonnes NBPT per year reported in the assessment as a new chemical are retained as a worst case scenario.

Of the 150 tonnes of NBPT imported, it can be assumed for the purpose of hazard assessment, that all is applied to soil through association with urea fertiliser. NBPT treated urea will be applied at rates similar to the rate of application of urea recommended for crop production.

10.1 Application rate

The rate of nitrogen which can be tolerated by crop seeds varies with the crop, soil type, moisture conditions at planting, the state of the seedbed, and the type of fertiliser (Coombs, 1994). As a guide, the maximum safe rate suggested for cereal crops in southern Australia at narrow row spacings under good planting conditions is 20 kg/ha of nitrogen. A maximum rate of nitrogen application (listed for clay soils) is 33 kg/ha (Coombs, 1994). This figure will be used for a worst case scenario.

Nitrogen comprises around 46% of urea (Coombs, 1994), and the maximum rate of 33 kg/ha nitrogen equates to 72 kg/ha urea. The notified substance is present in the final urea fertiliser at around 0.064%. This rate of application equates to a rate of 0.046 kg/ha of NBPT.

10.2 Birds

Application of the NBPT containing fertiliser is generally under the soil surface. This greatly reduces the exposure of the urea granules to birds. If applied as a top or side-dressing, the granules are likely to be hidden by plant cover. As such, it is unlikely that widespread consumption of granules will occur.

Birds may still be expected to ingest granules of AGROTAIN®-treated urea, either mistakenly for food, or a source of grit, with the extent of ingestion depending on both the availability of the granules to foraging birds, the characteristics of the granules and factors associated with bird behaviour (Best and Fisher, 1992). On average, granules weigh 13 mg and contain 0.064% (0.008 mg) of NBPT. If an omnivorous or granivorous bird were to consume 100 granules per day (NB: this is a very conservative assumption), and weighed 250 g, this is equivalent to 3.2 mg/kg bodyweight. While not a definitive toxicity test, hens are stated to have been shown to have an LD50 greater than 50 mg/kg bodyweight, and this calculation indicates a low hazard of NBPT to birds.

The company claims that NBPT is rapidly metabolised and excreted by birds, with about 30% of a 250 mg/kg dose being eliminated in the excreta within 24 hours. It

is also stated that there have been no reports of bird toxicity resulting from extensive use of AGROTAIN®-treated urea granules in the USA.

10.3 Soil invertebrates

An application rate of 0.046 kg/ha of the notified substance equates to around 0.07 mg/kg of soil in the top 5 cm of soil. While no figures are available as to the toxicity of NBPT to soil invertebrates, no adverse effects on earthworms have been observed during field testing. Based on the experience of Environment Australia, NBPT would need to be extremely toxic to present a hazard.

Additionally, NBPT has been shown to mineralise rapidly, with 50% mineralised between 8 and 16 days depending on soil types. It is unlikely that any NBPT will remain in the soil at the next application of urea.

10.4 Groundwater

The relatively high water solubility of NBPT gives the potential to leach to groundwater. The hydrolysis half life (at 25°C) of 92 days at pH 7, with a likely shorter half life as conditions become more acidic (pH3, t1/2=58 minutes) or basic (pH11, t1/2=16 days), may increase in groundwater where the temperature of the water would be somewhat lower. However, microbial activity which will occur in groundwater would be expected to lower the half life, and taking into account the fast rate of mineralisation in and proven ability of NBPT to bind to soil, this would combine to limit the extent of NBPT leaching to groundwater.

10.5 Aquatic species

Formulation is undertaken in closed buildings with waste trapping facilities at around 20 locations. Any material not absorbed to the urea granules will be washed from the mixing equipment and is likely to enter the sewer system.

The assessment as a new chemical estimated that an average quantity of AGROTAIN® formulated at each processing plant will be 30 tonnes per annum. Using this figure as a worst case release estimate, and assuming that 1% of the imported volume is lost to sewer during reformulation, this equates to 300 kg per year. Because the product needs to be used within two weeks of reformulation, it will be assumed that production takes place on 90 days per year. This equates to a daily release per plant of 3.3 kg, which if released to a country sewer with a daily output of 5 ML, would be in the sewage treatment plant at a concentration of 0.68 mg/L (ppm). Given the high degradation rate, possible adsorption of NBPT and its metabolites to soil, and the low toxicity to aquatic species (most sensitive effect of EC50=280 ppm to algae), a low environmental hazard to aquatic species from release during formulation is predicted.

Using the data provided for the secondary notification (1.1 tonnes of AGROTAIN® at each processing plant per annum) and a release rate of 1% of the imported volume, it is estimated that 11 kg per year is lost to sewer, 0.12 kg daily released per plant with a sewage concentration of 0.024 mg/L (ppm).

Run off to surface water during application is unlikely as the majority of the chemical is applied in granule form under ground. It is possible that in the future, the chemical may be applied with liquid fertilisers, or granules can be applied as a

top dressing, or surface applied as a pre-emergent application. As such, the potential for runoff exists.

As a worst case, it is assumed that of the application rate of 46 g/ha, 10% runs off due to rain or irrigation, to a 1 ha, 15 cm standing body of water. This would give a concentration of 3.1 µg/L (ppb) in the water body, which is several orders of magnitude lower than the most sensitive observed effect of EC50 equals 280 ppm to algae. Therefore, low aquatic hazard from use may be expected.

10.6 Conclusion

Risk characterisation shows low concerns for birds, soil invertebrates, ground water and aquatic species as a result of reformulation and end use activities of NBPT.

Appendix

The toxicological assessment of NBPT in NA/467 is reproduced here (NICNAS, 1997).

A.1 Acute Toxicity

Summary of the acute toxicity of NBPT

Test	Species	Outcome	Reference
acute oral toxicity (in distilled water)	rat (M)	LD50 > 4 200 mg/kg	Allied Corporation, 1984a
acute oral toxicity (in propylene glycol)	rat (M/F)	LD50 1 000-4 000 mg/kg	Allied Corporation, 1985
acute oral toxicity (in olive oil)	rat	LD50 > 2 000 mg/kg	North American Science Associates, 1990a
acute oral toxicity (87% NBPT in distilled water)	rat	LD50 > 2 823 mg/kg	Hazleton Wisconsin, 1994a
acute dermal toxicity	rabbit	LD50 > 2 000 mg/kg	North American Science Associates, 1990b
acute dermal toxicity	rabbit	LD50 > 2 000 mg/kg	Allied Corporation, 1984b
acute dermal toxicity	rabbit	LD50 > 2 000 mg/kg	Hazleton Wisconsin, 1994b
skin irritation	rabbit	not a classifiable irritant	Hazleton Wisconsin, 1994c
eye irritation	rabbit	*irritant	Corning Hazleton, 1996d
skin sensitisation	guinea pig	not classifiable as a dermal sensitiser	Allied Corporation, 1984c

* test substance AGROTAIN® (25% notified chemical)

A.1.1 Oral Toxicity (Allied Corporation, 1984a)

Species/strain:	Fischer 344 rats
Number/sex of animals:	5M/dose (500, 2 100, 4 200 mg/kg)
Observation period:	14 days
Method of administration:	gavage in distilled water
Clinical observations:	none
Mortality:	nil
Morphological findings:	none
Test method:	in accordance with TSCA GLP Regulations, similar to

	OECD guidelines
LD50:	> 4 200 mg/kg
Result:	low oral toxicity

A.1.2 Oral Toxicity (Allied Corporation, 1985)

Species/strain:	Fischer 344 rats
Number/sex of animals:	5M/5Fdose (300, 1 000, 4 000 mg/kg)
Observation period:	14 days
Method of administration:	gavage in propylene glycol
Clinical observations:	in 4.0 g/kg - hypoactivity, nasal discharge, audible and irregular respiration, lacrimation, miosis, salivation and hypothermia; significant decrease in body weight in 1 000 mg/kg males at day 1, also lower absolute heart weights and heart/body weight ratios; females 1 000 g/kg group had a lower spleen/body weight ratio
Mortality:	nil in 0.3 and 1.0 g/kg, 100% in 4 000 mg/kg
Morphological findings:	none
Test method:	in accordance with TSCA GLP Regulations, similar to OECD guidelines
LD50:	1 000-4 000 mg/kg
Result:	compound related effects and mortality at high doses; LD50 range too broad to define in relation to the Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004)

A.1.3 Oral Toxicity (North American Science Associates, 1990a)

Species/strain:	Sprague-Dawley rats
Number/sex of animals:	2M/3F at dose 2 000 mg/kg
Observation period:	7 days
Method of administration:	gavage in olive oil (10% w/v)
Clinical observations:	none
Mortality:	nil
Morphological findings:	none
Test method:	in accordance with FHSA regulations

LD50:	> 2 000 mg/kg
Result:	low oral toxicity

A.1.4 Oral Toxicity (Hazleton Wisconsin, 1994a)

Species/strain:	Crl:CD® (SD)BR rats
Number/sex of animals:	5M/5F dose of technical commercial product (87% NBPT)(M - 1 000, 2 500, 5 000 mg/kg, F - 1 000, 2 500, 3 000 mg/kg)
Observation period:	14 days
Method of administration:	gavage in distilled water
Clinical observations:	in surviving animals - thin appearance, hunched posture, staggered gait, hypoactivity, nasal discharge, lacrimation, miosis, salivation, absence of pain and righting reflex, prostration, stained face, dyspnea, bradypnea, soft stools, staining of urinogenital area
Mortality:	nil at low dose, 1 male 3 females at mid dose, 4 males and 3 females at high dose
Morphological findings:	none
Test method:	in accordance with USEPA standard with minor variations
LD50:	males 3 536, females 2 603, overall 2 823 mg/kg
Result:	low oral toxicity, symptoms common for cholinesterase inhibitors

A.1.5 Dermal Toxicity (North American Science Associates, 1990b)

Species/strain:	New Zealand white rabbits
Number/sex of animals:	3M/2F
Observation period:	7 days
Method of administration:	single dose of 2 000 mg/kg to intact and abraded skin
Clinical observations:	none
Mortality:	nil
Morphological findings:	None
Draize scores (Draize, 1959):	0
Test method:	in accordance with FHSA regulations

LD50:	> 2 000mg/kg
Result:	low dermal toxicity

A.1.6 Dermal Toxicity (Allied Corporation, 1984b)

Species/strain:	New Zealand white rabbits
Number/sex of animals:	3M
Observation period:	7 days
Method of administration:	single dose 2 000 mg/kg
Clinical observations:	none
Mortality:	nil
Morphological findings:	None
Draize scores (Draize, 1959):	0
Test method:	in accordance with TSCA GLP Regulations, similar to OECD guidelines
LD50:	> 2 000mg/kg
Result:	low dermal toxicity

A.1.7 Dermal Toxicity (Hazleton Wisconsin, 1994b)

Species/strain:	rabbit, New Zealand white
Number/sex of animals:	5M/5F
Observation period:	14 days
Method of administration:	single dose 2 000 mg/kg of technical commercial product (87% NBPT) occluded for 24 hours
Clinical observations:	slight to severe dermal irritation
Mortality:	nil
Morphological findings:	None
Draize scores (Draize, 1959):	0
Test method:	in accordance with TSCA GLP Regulations, similar to OECD guidelines
LD50:	> 2 000 mg/kg
Result:	low dermal toxicity

A.1.8 Skin Irritation (Hazleton Wisconsin, 1994c)

Species/strain:	rabbit New Zealand white
Number/sex of animals:	3M/3F
Observation period:	72 hours
Method of administration:	0.5g test material (87% pure) to intact skin on rabbits back, covered with gauze and overwrapped with Saran Wrap® for 4 hours
Draize scores (Draize, 1959):	only one animal had mild erythema at 24 hours which had gone by 48 hours
Test method:	in accordance with USEPA standard with minor variations
Result:	slight irritant, not classified as hazardous according to the Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004)

A.1.9 Eye Irritation of AGROTAIN (Corning Hazleton, 1996d)

Species/strain:	New Zealand white rabbits
Number/sex of animals:	6M/3F
Observation period:	21 days
Method of administration:	0.1 ml of test material (AGROTAIN®, 25% NBPT) in one eye, F eyes were flushed after 30 seconds, M unflushed

Draize scores of unirrigated eyes:

	Time after instillation									
Animal	**1 day**		**2 days**		**3 days**		**4 days**		**7 days**	
Cornea	**o[a]**	**a[b]**	**o[a]**	**a[b]**	**o[a]**	**a[b]**	**o[a]**	**a[b]**	**o[a]**	**a[b]**
1	11	4	1	3	1	1	0	0	0	0
2	1	3	1	3	1	3	1	1	0	0
3	1	4	1	3	1	2	1	1	0	0
4	1	4	1	3	1	2	1	1	0	0
5	1	3	1	2	1	1	1	1	1	1
6	1	2	1	2	1	1	0	0	0	0
Iris										
1	1		1		0		0		0	
2	1		1		1		1		0	
3	1		1		1		0		0	
4	1		1		1		1		0	
5	1		1		1		1		0	
6	1		0		0		0		0	
Conjunctiva	**r[c]**	**c[d]**	**d[e]**	**r[c]**	**c[d]**	**d[e]**	**r[c]**	**c[d]**	**d[e]**	**r[c]**	**c[d]**	**d[e]**	**r[c]**	**c[d]**	**d[e]**
1	2	2	2	2	1	0	2	1	0	2	1	0	1	1	0
2	2	2	2	2	2	2	2	2	1	2	2	1	2	1	0
3	2	2	2	2	2	2	2	1	0	2	1	0	2	1	0
4	2	1	2	2	1	0	2	1	0	2	1	0	1	1	0
5	2	2	2	2	2	1	2	2	1	2	2	1	2	2	0
6	2	1	2	2	1	0	2	1	0	2	1	0	1	1	0

1 see Attachment 1 for Draize scales; a opacity b area c redness d chemosis e discharge

	corneal opacity still present in rabbit #5 at day 21, conjunctival response still evident in 2 rabbits at day 14, all animals clear by day 21
Irrigated eyes:	produced positive irritation reactions (corneal, conjunctival and radial involvement) which cleared in last animal by day 7
Test method:	in accordance with USEPA standard
Result:	eye irritant, classified as hazardous according to the Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) on the basis of iris lesion mean value over all animals of 1 or more which present for 24 hours or more; effects were still evident in one rabbit at day 21

A.1.10 Skin Sensitisation (Allied Corporation, 1984c)

Species/strain:	Hartley guinea-pig
Number of animals:	15 in test group, 6 negative control group
Induction procedure:	day 1, 3 pairs of intradermal injections, Freunds Complete Adjuvant (FCA) alone with test article and vehicle (distilled water); day 7 mildly irritating concentration of test article applied to test area on patch for 48 hours
Challenge procedure:	day 21 patch applied to test site with either vehicle or test article in vehicle for 24 hours; readings taken 24 hours after patch removal

2nd Challenge outcome:

Challenge concentration	**Test animals**		**Control animals**	
	24 hours*	**48 hours***	**24 hours**	**48 hours**
10% w/v in propylene glycol	**2/15	2/15	0/3	0/3

* time after patch removal
** number of animals exhibiting positive response

Test method:	in accordance with TSCA GLP Regulations, similar to OECD guidelines
Result:	13% positive response which is below the 30% threshold for adjuvant type test methods, therefore not a skin sensitiser according to the Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004)

A.2 Repeated Dose Toxicity (Hazleton Laboratories, 1990a)

Species/strain:	Sprague-Dawley rat
Number/sex of animals:	5M/5F per dose group
Method of administration:	oral gavage as a suspension of 0.5% methylcellulose in distilled water
Dose/Study duration::	0, 250, 500, 1 000 and 2 000 mg/kg/day for 15 days
Clinical observations:	1 000 and 2 000 mg/kg dose groups exhibited salivation and languid behaviour
Clinical chemistry/Haematology	500 mg/kg females and both sexes in higher dose groups had a decrease in blood urea nitrogen; total cholesterol decreased in high dose animals; triglycerides decreased in high dose males; alanine aminotransferase increased in 500 and 1 000 mg/kg males; brain and erythrocyte cholinesterase levels were decreased for all animals in two high dose groups; decreased erythrocyte cholinesterase levels also evident in 500 mg/kg animals
Histopathology:	spleen weight decreased for high dose females and spleen/body weight ratios decreased for all high dose animals
Test method:	not specified; however test duration does not conform to OECD guidelines
Result:	significant effects at a dose of 500 mg/kg/day; clinical chemistry and haematology results suggest that the liver is the target organ (without cholestasis); liver weight was not effected, however the study was of limited duration (15 days)

A.3 Genotoxicity

A.3.1 Salmonella typhimurium Reverse Mutation Assay (Allied Corporation, 1984d)

Strains:	TA 100, TA 98, TA 1535, TA 1537 with and without metabolic activation (S-9)
Concentration range:	0.1, 0.5, 1.0, 2.5 and 5.0 mg/L
Test method:	similar to OECD guidelines
Result:	not mutagenic in this system

A.3.2 Salmonella typhimurium Reverse Mutation Assay (Hazleton Washington, 1990)

Strains:	TA 100, TA 98, TA 1535, TA 1537 with and without metabolic activation (S-9)
Concentration range:	333, 667, 1 000, 3330, 5 000 μg/plate
Test method:	similar to OECD guidelines
Result:	not mutagenic in this system

A.3.3 Micronucleus Assay in the Bone Marrow Cells of the Mouse (Hazleton Laboratories, 1990b)

Species/strain:	mouse, ICR
Number and sex of animals:	5M/5F per dose group
Doses:	100, 333, 1 000 mg/kg
Method of administration:	in corn oil via intraperitoneal injection
Test method:	similar to OECD guidelines
Result:	not clastogenic in this system

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