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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

n-(n-butyl) thiophosphoric triamide

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

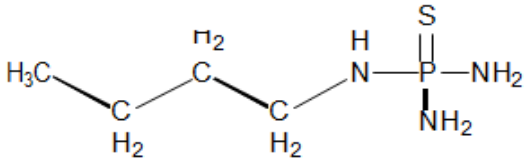
n-(n-butyl) thiophosphoric triamide

1. APPLICANT

AGROW Australia Pty Ltd of 231 Miller Street NORTH SYDNEY 2060 has submitted a standard notification statement in support of their application for an assessment certificate for n-(n-butyl) thiophosphoric triamide.

2. IDENTITY OF THE CHEMICAL

The notifier has not requested that any information be exempted from the Full Public Report.

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® (notified chemical is 25% of this formulation)
Molecular Formula:	$C_4H_{14}N_3PS$
Structural Formula:	

Molecular Weight:	167.2
Method of Detection and Determination:	reverse-phase high pressure liquid chromatography (HPLC) with ultra violet (UV) detection
Spectral Data:	the submission included suitable validation of the analytical method (1)

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	white crystalline solid
Melting Point:	58-60°C
Density:	1.036 g/mL
Vapour Pressure:	1.067 kPa at 40°C
Water Solubility:	4 300 mg/L at 25°C
Partition Co-efficient (n-octanol/water):	log P_{ow} = 0.415 (test report unsighted)
Hydrolysis as a Function of pH:	$T_{1/2}$ at pH 3.0 = 58 minutes at 25°C $T_{1/2}$ at pH 7.0 = 92 days at 25°C $T_{1/2}$ at pH 11.0 = 16 days at 25°C
Adsorption/Desorption:	not determined
Dissociation Constant:	not determined
Flash Point:	96°C (closed cup)
Flammability Limits:	Upper Explosive Limit (AGROTAIN®)= 17.4 % (as propylene glycol) Lower Explosive Limit (AGROTAIN®)= 1.3 % (as n-methyl pyrrolidone)
Autoignition Temperature:	not determined
Explosive Properties:	not considered explosive although the closed plastic shipping containers containing AGROTAIN® may rupture due to a build-up of pressure when exposed to extreme heat

Reactivity/Stability: stable and unreactive at normal temperatures

Comments on Physico-Chemical Properties

The mean density was determined during water solubility testing. The figure provided above is that of an aqueous saturated n-(n-butyl) thiophosphoric triamide (NBPT) solution after 66 hours of agitation.

Solubility was tested to meet the requirements of the USEPA Pesticide Assessment Guidelines Subdivision D, Series 63-8, and followed the broader guidance provided in TSCA requirements specified in 40 CFR 796.1840. Determination of solubility was directly by radioassay of aliquots by liquid scintillation counting. HPLC analysis demonstrated the substance was stable in water for the duration of the experiment.
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 partition co-efficient is stated as log P_{ow} = 0.415, although no test report is provided to substantiate this. The low value is expected due to the high water solubility of the notified substance.

No adsorption/desorption test was provided. Based on the relatively high water solubility, adsorption would be expected to be low. Some complexation to clay particles may occur. Adsorption is discussed further in the Environmental Fate section below.

4. PURITY OF THE CHEMICAL

Degree of Purity: 85%

Toxic or Hazardous Impurities: the notifier claims there is no indication that any of the impurities identified in the technical product are toxic; this is based on the observation that the technical NBPT with impurities has the same level of toxicity as the purified material

Chemical name:	tetrahydrofuran
CAS No.:	109-99-0
Weight percentage:	0-2%
Toxic properties:	irritant; threshold for classification of a mixture as hazardous according to Worksafe Australia's *List of Designated Hazardous Substances* (2), 25%

Chemical name:	triethylamine
CAS No.:	121-44-8
Weight percentage:	0-2%
Toxic properties:	irritant; threshold for classification of a mixture as hazardous according to Worksafe Australia's *List of Designated Hazardous Substances* (2), 25%

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

Chemical Name	*CAS No.*	*Weight %*
N,N-di-(n-butyl) thiophosphoric triamide (DNBPT)		0-3%
N,N,N-tri-(n-butyl) thiophosphoric triamide (TNBPT)		0-1%
thiophosphoric triamide (TPT)		0-3%
Other (eg. dimers and more complex materials)		0-10%

Additives/Adjuvants: the formulation AGROTAIN® contains 25% of the notified chemical, 60-65% of unspecified non-hazardous ingredients, the other 10% consists of:

Chemical name:	n-methyl pyrrolidone
Synonyms:	n-methyl-2-pyrrolidone
CAS No.:	872-50-4
Weight percentage:	10%

N-methyl pyrrolidone is an irritant (2) and has workplace exposure standard of 3 ppm (mg/m^3) listed in Worksafe Australia's *Exposure Standards for Atmospheric Contaminants in the Occupational Environment* (3). The threshold for classification of a mixture as hazardous is 10 % according to Worksafe Australia's *List of Designated Hazardous Substances* (2); therefore the formulation AGROTAIN® is classified as hazardous on this basis.

5. USE, VOLUME AND FORMULATION

The notified chemical will not be manufactured in Australia.

AGROTAIN® containing the notified chemical will be imported to Australia in 9.46 L (2.5 US gallon) sealed containers where it will be transported to approximately 20 centres for reformulation.

Import volumes of AGROTAIN® (which contains the notified chemical at around 25%) are expected to be 120 tonnes (30 tonnes of the notified chemical) initially, rising to over 600 tonnes (150 tonnes notified product) within 3 to 5 years. Larger quantities may be imported in subsequent years.

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 new 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, NBPT will be used initially in combination with granular urea; subsequently it may be used with urea ammonium nitrate (UAN) liquid fertilisers. NBPT in the form of AGROTAIN® will be added to granular urea to give a maximum concentration of 0.2% w/w NBPT, and to UAN at a rate up to 0.3% w/w of the urea content in UAN.

6. OCCUPATIONAL EXPOSURE

The notified chemical will only be imported as a 25% constituent of the formulation AGROTAIN®. This is a liquid and will be packaged in 9.46 L containers. This will be transported to reformulating facilities for application to granular urea fertilisers. Occupational exposure during transport, unloading and warehousing of AGROTAIN® will be limited to accidental release and any subsequent exposure.

Potential occupational exposure to the notified chemical will be greatest during application to the granulated fertiliser and to a lesser extent during fertiliser usage. During the process of application of AGROTAIN® (containing 25% NBPT) to the granulated urea fertiliser, exposure will be to a much higher concentration than during usage of the fertiliser which will contain only 0.2% w/w of the notified chemical. At the reformulation sites, AGROTAIN® will be decanted from the plastic drums into spraying equipment for application to the granular urea. Impregnation of urea with the AGROTAIN® concentrate should be done prior to bulk blending with any other fertiliser components. After spraying over the 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 will be involved in the reformulation process. Their exposure will be limited by the provision of rubber gloves, long sleeved clothing and eye protection. The main exposure pathways will be dermal and ocular although there will also be limited potential for inhalational exposure via mists or dusts. Dusts maybe generated during bagging and transferral of treated urea, the low concentration of the notified chemical (0.02%) in this product will limit exposure.

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

Farmers/applicators will transfer the treated fertiliser from farm storage areas to application equipment (spreaders, drills etc.). The fertiliser may be either broadcast or applied to the subsoil. Exposure to the notified chemical will again be 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 (4). Exposure estimates using this model are of the order of 0.0069 mg/kg/day.

7. PUBLIC EXPOSURE

AGROTAIN® in liquid form containing 25% of the notified chemical will be imported and transported to customers for reformulation in enclosed areas at industrial plants. No public exposure is expected to occur during the reformulation process.

Fertilisers containing the notified chemical will be available to farmers and possibly the general public to be applied to topsoil or subsoil by spreaders, drills or other equipment. Public exposure to the notified chemical by dermal contact may occur.

The notified chemical 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%. The notified chemical 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, 0.114 kg/ha of the notified chemical; therefore, residues of the notified chemical 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 the notified chemical. However, public exposure will be minimal if the spills are properly contained.

8. ENVIRONMENTAL EXPOSURE

Release

At the reformulation sites, AGROTAIN® (containing 25% of the notified product) will be applied to granular urea. Impregnation of urea with the AGROTAIN®

concentrate should be 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 is expected to remain in 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 will be minimal, with the cost of the material ensuring as little as possible remains in containers. Drums are likely to be either sent to secure landfill, or recycled.

After mixing, the end product (containing the notified product at around 0.2% w/w) is transported to farms in either 50 kg bags, 1 tonne bulk bags, or in bulk. It is expected that bulk shipment will be by far the main method, increasing exposure in the case of accidental spillage.

During end use, all notified product will be 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 will be applied at rates similar to the rate of application of urea recommended for crop production (discussed in the Environmental Hazard Section below).

No home garden use of this product is anticipated.

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

Fate

NBPT is to be imported into Australia for incorporation into granular urea, and possibly 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, the urease inhibition cannot last for extended periods of time.

The notified chemical will be 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 Section 11). 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 parent compound or metabolites of NBPT. The test does demonstrate that bound residues of NBPT are formed in soil.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Summary of the acute toxicity of NBPT

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity (in distilled water)	rat (M)	LD_{50} > 4 200 mg/kg	5
acute oral toxicity (in propylene glycol)	rat (M/F)	LD_{50} 1 000-4 000 mg/kg	6
acute oral toxicity (in olive oil)	rat	LD_{50} > 2 000 mg/kg	7
acute oral toxicity (87% NBPT in distilled water)	rat	LD_{50} > 2 823 mg/kg	8
acute dermal toxicity	rabbit	LD_{50} > 2 000 mg/kg	9
acute dermal toxicity	rabbit	LD_{50} > 2 000 mg/kg	10
acute dermal toxicity	rabbit	LD_{50} > 2 000 mg/kg	11
skin irritation	rabbit	not a classifiable irritant	12
eye irritation	rabbit	*irritant	13
skin sensitisation	guinea pig	not classifiable as a dermal sensitiser	14

* test substance AGROTAIN® (25% notified chemical)

9.1.1.1 Oral Toxicity (5)

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 (15)
LD_{50}:	> 4 200 mg/kg
Result:	low oral toxicity

9.1.1.2 Oral Toxicity (6)

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 (15)
LD_{50}:	1 000-4 000 mg/kg
Result:	compound related effects and mortality at high doses; LD_{50} range too broad to define in relation to Worksafe Australia's *Approved Criteria for Classifying Hazardous Substances* (16)

9.1.1.3 Oral Toxicity (7)

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 (17)
LD_{50}:	> 2 000 mg/kg
Result:	low oral toxicity

9.1.1.4 Oral Toxicity (8)

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 (18)

LD_{50}:	males 3 536, females 2 603, overall 2 823 mg/kg
Result:	low oral toxicity, symptoms common for cholinesterase inhibitors

9.1.2.1 Dermal Toxicity (9)

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 (19):	0
Test method:	in accordance with FHSA regulations (17)
LD_{50}:	> 2 000mg/kg
Result:	low dermal toxicity

9.1.2.2 Dermal Toxicity (10)

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 (19):	0
Test method:	in accordance with TSCA GLP Regulations,

	similar to OECD guidelines (15)
LD_{50}:	> 2 000mg/kg
Result:	low dermal toxicity

9.1.2.3 Dermal Toxicity (11)

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 (19):	0
Test method:	in accordance with TSCA GLP Regulations, similar to OECD guidelines (15)
LD_{50}:	> 2 000 mg/kg
Result:	low dermal toxicity

9.1.3 Skin Irritation (12)

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 (19):	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 (17)

Result:	slight irritant, not classified as hazardous according to Worksafe Australia's *Approved Criteria for Classifying Hazardous Substances* (15)

9.1.4 Eye Irritation (13)

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 (19) 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	[1]1	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 (20)

Result: eye irritant, classified as hazardous according to Worksafe Australia's *Approved Criteria for Classifying Hazardous Substances* (16) 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

9.1.5 Skin Sensitisation (14)

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:

	Test animals		***Control animals***	
Challenge concentration	***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 (15)

Result: 13% positive response which is below the 30% threshold for adjuvant type test methods, therefore not a skin sensitiser according to Worksafe Australia's *Approved Criteria for Classifying Hazardous Substances* (16)

9.2 Repeated Dose Toxicity (21)

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 (15)
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)

9.3 Genotoxicity

9.3.1.1 *Salmonella typhimurium* Reverse Mutation Assay (22)

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 (15)
Result:	not mutagenic in this system

9.3.1.2 *Salmonella typhimurium* Reverse Mutation Assay (23)

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 (15)
Result:	not mutagenic in this system

9.3.2 Micronucleus Assay in the Bone Marrow Cells of the Mouse (24)

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 (15)
Result:	not clastogenic in this system

9.4 Overall Assessment of Toxicological Data

The notified chemical is not considered toxic via dermal exposure or ingestion with LD_{50} values for rats in excess of 2 000 mg/kg. This was demonstrated in a range of studies with various carriers. The chemical has some potential for skin irritation, in a study using rabbits minor effects were evident but were reversible. The effects were below the level requiring a hazardous classification according to the criteria of Worksafe Australia (16). Data on eye irritation potential was only available for the imported commercial formulation AGROTAIN®. In a rabbit study (eyes were unwashed) reversible effects (by 21 days) which included effects on the conjunctiva, cornea and iris were significant enough to fulfil the requirements for a hazardous classification (irritant). In addition one of the rabbits tested still had corneal opacity at 21 days. On this basis the formulation is classified as hazardous according to the criteria of Worksafe Australia and in the absence of further data for the notified chemical this is also considered to be hazardous.

A skin sensitisation study using guinea-pigs found that the notified chemical was not a skin sensitiser. A repeat dose study with a duration of 15 days indicated that the probable target organ is the liver. Clinical chemistry and haematology results; 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; suggest that the liver is the target organ (without cholestasis); liver weight was not effected. The spleen body weight ratio was also effected in high dose animals. Dose related effects were evident at doses of 500 mg/kg/day and above.

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

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The following ecotoxicity studies have been supplied by the notifier. The tests were carried out according to OECD Test Methods (15).

Ecotoxicity Test Results:

Test	Species	Results (mg/L)
Acute Toxicity (S; N)	Bluegill (*Lepomis macrochirus*)	96 h LC_{50}=1 140
Immobilisation (S; N)	Water Flea (*Daphnia magna*)	48 h EC_{50}=290
Growth Inhibition (S; N)	Algae (*Selenastrum capricornutum*)	96 h EC_{50}=280

S=Static; N=Nominal Concentration.

At all concentrations tested, (700, 1 100, 1 800, 3 000 and 5 000 ppm) sub-lethal or lethal effects to fish were observed. At 700 and 1 100 ppm, the noted effects were largely lethargy, while above this concentration, effects were primarily lethal.

Two end points, immobilisation and death were used during daphnia testing. Using probit analysis, the 48 hour LC_{50} equals 350 ppm, while the 48 hour EC_{50} (immobilisation) of 290 ppm was obtained using nonlinear interpolation.

Using probit analysis, the values of EC_{10} equals 110 ppm, EC_{50} equals 280 ppm and EC_{90} = 760 ppm were obtained for algae. These data relate to growth rate, with results determined by cell count.

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

Similarly, no definitive avian toxicity studies have 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 LD_{50} of greater than 50 mg/kg bodyweight to hens.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

Of the potential 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.

- 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 (25). 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 (25). This figure will be used for a worst case scenario.

Nitrogen comprises around 46% of urea (25), 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 0.2%. This rate of application equates to a rate of 0.114 kg/ha of the notified substance.

- 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 (26). On average, granules weigh 13 mg and contain 0.2% (0.026 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 10.4 mg/kg bodyweight. While not a definitive toxicity test, hens are stated to have been shown to have an LD_{50} 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.

- Soil invertebrates

An application rate of 0.114 kg/ha of the notified substance equates to around 0.175 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, the notified substance 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.

- Groundwater

The relatively high water solubility of the notified substance 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, $t_{1/2}$=58 minutes) or basic (pH11, $t_{1/2}$=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 notified chemical leaching to groundwater.

- 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 average quantity of AGROTAIN® formulated at each processing plant will be 30 tonnes per annum. As a worst case release estimate, it will be assumed 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 0.67 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 EC_{50}=280 ppm to algae), a low environmental hazard to aquatic species from release during formulation is predicted.

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 114 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 7.6 µg/L (ppb) in the water body, which is several orders of magnitude lower than the most sensitive observed effect of EC_{50} equals 280 ppm to algae. Therefore, low aquatic hazard from use may be expected.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The notified chemical is classified as hazardous on the basis of an eye irritation study on the imported commercial formulation AGROTAIN®. This formulation contains only 25% of the notified chemical and 10% of a known irritant, n-methyl pyrrolidone. 10% n-methyl pyrrolidone is the threshold requiring a hazardous classification (irritant) according to Worksafe Australia's List of Designated Hazardous Substances (2). It could be argued that the notified chemical is not an eye irritant however in the absence of an eye irritation study specifically on the notified chemical, the hazardous classification remains. All other toxicity data submitted indicates that the notified chemical is of low toxicological concern. It has

a low oral and dermal toxicity, is not considered a skin irritant or sensitiser and gave negative results in an Ames mutagenicity study and an *in vivo* mouse micronucleus assay. It should be noted that in the skin irritation study there was evidence of irritation, however the levels were below that requiring a hazardous classification (15).

The highest level of occupational exposure is likely to be during reformulation. Although subsequent occupational exposure during fertiliser usage maybe for longer time periods the concentration will be lower (0.02%) compared to the 25% concentration of notified chemical in the imported formulation AGROTAIN®. Up to 100 employees will potentially be exposed to the notified chemical during reformulation. Dermal and ocular exposure will be the most likely pathways although any exposure will be limited by enclosed reformulating equipment, clothing and personnel protective equipment. On the basis of the submitted data on reformulation, toxicity and potential exposure, risk to workers undertaking reformulation will be minimal if the appropriate personal protective equipment is used.

Exposure during application by agricultural workers will minimal. The notifier has provided an estimate based on a pesticide exposure model of 0.0069 mg/kg/day. although the notifier's estimate of margin-of-safety is open to criticism as it based on a 15 day repeat dose study to determine chronic effects, it still indicates a considerable safety margin for agricultural workers. It is considered that the risk associated with usage of the notified chemical by agricultural workers is low.

Urea fertilisers containing the notified chemical will be used by farmers and may be available to the public. Public exposure can occur during application of the fertilisers. Although the notified chemical is an organophosphate and a severe eye irritant in rabbits, the low level (0.2%) present in the fertilisers is not expected to lead to a significant hazard. Residues of the notified chemical in food commodities are expected to be negligible.

13. RECOMMENDATIONS

To minimise occupational exposure to n-(n-butyl) thiophosphoric triamide the following guidelines and precautions should be observed when handling the notified chemical as the imported formulation AGROTAIN®:

- Safety goggles should be selected and fitted in accordance with Australian Standard (AS) 1336 (27) to comply with Australian/New Zealand Standard (AS/NZS) 1337 (28);
- Industrial clothing should conform to the specifications detailed in AS 2919 (29) and AS 3765.1 (30);
- Impermeable gloves or mittens should conform to AS 2161 (31);
- All occupational footwear should conform to AS/NZS 2210 (32);

- Spillage of the notified chemical should be avoided, spillages should be cleaned up promptly with absorbents which should then be put into containers for disposal;

- Good personal hygiene should be practised to minimise the potential for ingestion;

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

In addition:
- if the notified chemical is likely to leave detectable residue levels in food commodities, the company should submit an appropriate application to the Australian and New Zealand Food Authority for the establishment of an appropriate entry into the Food Standards Code.

14. MATERIAL SAFETY DATA SHEET

The MSDS for the notified chemical was provided in accordance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (33).

This MSDS was provided by the applicant as part of the notification statement. It is reproduced here as a matter of public record. The accuracy of this information remains the responsibility of the applicant.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the Act, secondary notification of the notified chemical shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise. In addition the company agrees to provide the Environmental Protection Group of Environment Australia with any information that it becomes aware of, either in Australia or overseas, to indicate a likelihood of unintended adverse effects on the environment, particularly relating to birds or soil invertebrates.

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Attachment 1

The Draize Scale for evaluation of skin reactions is as follows:

Erythema Formation	*Rating*	*Oedema Formation*	*Rating*
No erythema	0	No oedema	0
Very slight erythema (barely perceptible)	1	Very slight oedema (barely perceptible)	1
Well-defined erythema	2	Slight oedema (edges of area well-defined by definite raising	2
Moderate to severe erythema	3	Moderate oedema (raised approx. 1 mm)	3
Severe erythema (beet redness)	4	Severe oedema (raised more than 1 mm and extending beyond area of exposure)	4

The Draize scale for evaluation of eye reactions is as follows:

CORNEA

Opacity	*Rating*	*Area of Cornea involved*	*Rating*
No opacity	0 none	25% or less (not zero)	1
Diffuse area, details of iris clearly visible	1 slight	25% to 50%	2
Easily visible translucent areas, details of iris slightly obscure	2 mild	50% to 75%	3
Opalescent areas, no details of iris visible, size of pupil barely discernible	3 moderate	Greater than 75%	4
Opaque, iris invisible	4 severe		

CONJUNCTIVAE

Redness	*Rating*	*Chemosis*	*Rating*	*Discharge*	*Rating*
Vessels normal	0 none	No swelling	0 none	No discharge	0 none
Vessels definitely injected above normal	1 slight	Any swelling above normal	1 slight	Any amount different from normal	1 slight
More diffuse, deeper crimson red with individual vessels not easily discernible	2 mod.	Obvious swelling with partial eversion of lids	2 mild	Discharge with moistening of lids and adjacent hairs	2 mod.
Diffuse beefy red	3 severe	Swelling with lids half-closed	3 mod.	Discharge with moistening of lids and hairs and considerable area around eye	3 severe
		Swelling with lids half-closed to completely closed	4 severe		

IRIS

Values	*Rating*
Normal	0 none
Folds above normal, congestion, swelling, circumcorneal injection, iris reacts to light	1 slight
No reaction to light, haemorrhage, gross destruction	2 severe