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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Tin Butyl mixed thiol complexes (Thermolite 178)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Water Resources.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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FULL PUBLIC REPORT

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Arkema Pty Ltd (ABN 44 000 330 772)
Ground Floor, 600 Victoria Street
RICHMOND VIC 3121

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: Chemical Name, CAS Number, Molecular Formula, Structural Formula, Molecular Weight, Spectral Data, Purity, Concentration in Use, Import Volume, Identity of Recipients

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:
Hydrolysis as a function of pH, Partition Coefficient, Explosive properties, Reactivity, Some toxicological endpoints

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
CEC/723
CER/8

NOTIFICATION IN OTHER COUNTRIES
Canadian (1999) USA (Year unknown)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
THERMOLITE 178 (product containing the notified chemical)

OTHER NAME(S)
Complex organotin mercaptol sulfide

ANALYTICAL DATA
Reference infrared spectra were provided.

BREAKDOWN PRODUCT
The notified chemical is used to scavenge the released HCl in the polyvinyl chloride (PVC). The reaction with the HCl and organotin stabiliser produced alkyltin chloride (monobutyltin trichloride), alkyl thiol and 2-mercaptoethanol.

3. COMPOSITION

DEGREE OF PURITY > 90%

MOLECULAR WEIGHT > 650 Da

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% by weight)

None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Clear, pale yellow liquid

Property	Value	Data Source/Justification
Freezing Point	-18°C	Measured
Boiling Point	Excessive foaming at 181°C	Measured, no reflux temperature was obtainable.
Density	1010 kg/m^3 at 25°C	MSDS
Vapour Pressure	1.65 kPa at 25°C	Measured
Water Solubility	< 0.3 g/L at 20°C	Estimated
Hydrolysis as a Function of pH	Hydrolysable	Based on its chemical structure and the reactivity of similar compounds.
Partition Coefficient (n-octanol/water)	Not determined	The water-oil partitioning constant is expected to be high based on the notified chemical's low solubility in water and high solubility in hydrocarbons.
Adsorption/Desorption	Not determined	The notified chemical is expected to partition to soil and sludge based on its low solubility in water and chemical structure.
Dissociation Constant	Not determined	The notified chemical does not contain any (acidic or basic) dissociable groups.
Particle Size	Not applicable	The chemical is a liquid over the normal environmental temperature range.
Flash Point	140°C (Closed cup)	MSDS for product containing 50% notified chemical
Flammability	Upper: 10.4% at 250°C Lower: 0.82% at 250°C	Measured
Autoignition Temperature	257-260 °C	Measured
Explosive Properties	Not determined	The notified chemical does not contain typically explosive groups.

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties, please refer to Appendix A.

Reactivity
The notified chemical is stable under normal conditions and does not react with air. Prolonged exposure to water may cause slow hydrolysis of the product.
The notified chemical is used as heat stabiliser to prevent degradation by heat during processing at high temperatures. It acts by scavenging the evolved HCl via an irreversible chemical reaction. As a result, alkyltin chloride and free mercaptan are produced (i.e., monobutyltin trichloride, alkyl thiol and 2-mercaptoethanol).

Dangerous Goods classification
Based on the available data the product containing 50% notified chemical is classified as follows according to the Australian Dangerous Goods Code (FORS, 1998):

C1 combustible liquid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
Imported as a 50% solution in hydrocarbon solvent in 200 L drums by full container load (FCL) delivered to ARKEMA.

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 100	< 200	< 200	< 200	< 200

PORT OF ENTRY
Brisbane and Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
Imported by ARKEMA Pty Ltd

TRANSPORTATION AND PACKAGING
Thermolite 178 containing 50% of the notified chemical is imported in 200 L drums in Mixed FCL. The container is transported from the wharf to a dangerous goods warehouse facility and unloaded by forklift for storage in a bunded drum farm before dispatch to PVC manufacturers. Typically T178 is transported using a pallet of 4 drums to customers.

USE
Stabiliser (at up to 1%) in granulated PVC used to manufacture sewerage pipes, drainage pipes, electrical pipes, potable water pipes and other construction applications (for external use). The predominant use is in the manufacture of pipe, where it is generally buried underground but can include downpipes and electrical conduit (rigid pipe). Potable water pipe would be a very small use.

OPERATION DESCRIPTION
At the customer site, the premix worker connects the metering pump to the drum of the notified chemical and ensures the correct composition of the premix to be fed into the compounding extruder. The drum of the notified chemical is set up to automatically pump a measured quantity of the notified chemical into a premix of additives that are to be added to each batch of compounded plastic.

Typically the manufacture of a batch of fully compounded PVC is < 1000 kg containing ≈ 10% premix and < 1% notified chemical. Virgin PVC resin is mixed in a compounding extruder with a premix consisting of pigments, fillers, process aids, processing lubricant wax and the notified chemical.

In the compounding extruder the premix containing the notified chemical is gravity fed directly into the preheat mixing zone and as it progressively enters the extruder it is coarsely mixed under increasingly high shear and increased temperature (between 150 and 190ºC) with virgin resin until the PVC and premix become a homogeneous molten plastic blend, with the notified chemical being at a concentration of < 1%. The molten blend or PVC compound is then forced through an extrusion die that creates spaghetti that is chopped by rotating knives into small pellets and cooled on a conveyer of similar before being captured in a finished product bin ready for yet another extrusion process to make the final form or object.

PVC granules containing the notified chemical at up to 1% will then be extrusion moulded to produce PVC articles such as pipes.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport driver	20	4 hours/day	10 days/year
Storeman	10	0.5 hours/day	40 days/year
Premix worker	9	0.25 hours/day	320 days/year
Compounding extruder operator	9	8 hours/day	320 days/year
Article extruder operator	9	8 hours/day	320 days/year

Transport and storage
Transport drivers and storemen would only be exposed to the notified chemical in the unlikely event of a spillage.

Dermal exposure to 50% notified chemical may occur when connecting the pipes to drums containing the notified chemical. The remainder of the process will be automated and therefore workers' exposure at that stage will be limited. Dermal uptake is limited by the high molecular weight of the notified chemical and its low water solubility.

Dermal exposure to the notified chemical can be estimated based on the EASE model using reasonable worst case defaults for a particular activity (European Commission, 2003) as follows:

Activity	*Estimated exposure for activity <mg/day>*	*Estimated exposure for notified chemical <mg/kg bw/day>**
Manual addition of liquids	420	6
Coupling and decoupling of transfer line	42	0.6

*for a 70 kg worker and a 100% dermal absorption factor

Inhalation exposure by premix workers and compounding extruder operators may occur as the notified chemical has a low to moderate vapour pressure. After blending with PVC resin, inhalation of dust particles containing adsorbed notified chemical at < 1% is possible. Workers are expected to wear thick heat and chemical resistant gloves, heat resistant clothing and heavy work boots. The mixing vessel is fitted with local exhaust ventilation and is enclosed so that exposure of workers is unlikely during high-speed mixing. Local exhaust ventilation is employed during packing and some dermal contact may be possible from spillage.

There is potential for inhalation of the PVC particles which the notified chemical is adsorbed into during transfer and cleaning operations and this is controlled by the use of respirators and local exhaust ventilation.

Thermal degradation may occur during the compounding and extrusion processes. The notified chemical may degrade into lower molecular weight organotin and thiol molecules as part of its function as a stabiliser. However, inhalation exposure is limited as air exhausts are expected to be employed. The notifier has stated that the level of thermal degradation is very low unless there is a long residence time in the barrel of the extruder, normally degradation will be < 0.01% wt.

Extrusion of articles

In the manufacture of PVC articles, the granules are loaded to the extruder, heated to melt the plastic and extruded into the desired shape. Workers may be exposed to PVC dust from the granules (size unknown), containing < 1% of the notified chemical. During moulding the notified chemical may undergo further partial thermal degradation to smaller organotin and thiol molecules. Once the extruded articles are produced, dermal exposure to the notified chemical is possible if migration of the notified chemical from the granulated PVC occurs. However, as this stage is automated and engineering controls are in place, exposure is likely to be low.

Information on occupational exposure from the literature

It is difficult to estimate what level of occupational exposure to the notified chemical and/or its breakdown products may occur during the range of conditions occurring in different PVC compounding and extrusion plants. Personal air monitoring for organotin compounds was carried out at several USA and Canadian plants during PVC manufacture (Boraiko and Batt, 2005). Personal air samples were collected in the breathing zone of workers carrying out tasks such as mixing/blending, milling of PVC compound, pelletising and extrusion and the results compared to the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV) for organic tin compounds of 0.1 mg/m^3 as tin. . Local and general exhaust and ventilation systems were operating during the monitoring periods. The highest levels in air were found during manual processes (usually involving tasks conducted infrequently), such as opening and closing of drums of tin stabiliser and connecting and disconnecting pumps to these drums, pouring of tin stabiliser into containers to be added manually to a batch of PVC being compounded, cleaning up small residuals from the tops of drums or from the dip pipe after removing the pump dip pipe from the drum, sampling of stabilisers for analysis at the time of bulk delivery, connecting and disconnecting hoses at the time of bulk delivery and cleaning up any small residuals remaining after delivery and cleaning mixing vessels or continuous lines after use for PVC compounding. Under the conditions of the survey greater potential for exposure was found to occur during manual processes than during processes including more automation and engineering controls.

6.1.2. Public exposure

Exposure to the notified chemical as imported
The notified chemical, imported as a 50% solution, will only be sold to industrial customers, and so public exposure is not expected.

Migration of the notified chemical from PVC articles
The notified chemical will be incorporated into PVC articles, with which the public are expected to experience direct exposure (e.g. dermal) or indirect exposure (e.g. through potable water). The notified chemical is expected to have a high diffusibility within PVC, due to its use as a stabiliser, and so its migration from PVC is probable. Such leaching is expected to be temperature-dependent, due to changes in the structure of the polymer matrix leading to changes in mobility of solutes within it (i.e. higher mobility at higher temperatures).

Given the expected high $logP_{ow}$ of the notified chemical, in a predominantly dry environment (such as ambient conditions around buildings) it is expected to largely remain dissolved in the PVC polymer matrix. Transient contact with water (e.g. rain) is not expected to result in significant extraction of the notified chemical, but where prolonged contact occurs (e.g. water storage in PVC), the level of notified chemical in water might approach its degree of solubility (< 0.3 g/L at 20ºC, in the absence of hydrolytic degradation). Prolonged exposure of PVC articles to hydrophobic solvents might result in significant extraction, but this is, however, not an expected occurrence.

Dermal exposure to the notified chemical from PVC articles
The level of notified chemical available to cause exposure on the contact surface of a PVC article is not expected to approach its level of incorporation (< 1%), even at elevated temperatures. A worst-case dermal exposure estimate has been calculated for the notified chemical by Health Canada, based on a conservative estimation of its diffusion coefficient (Kp) in a low-viscosity solvent. This estimate assumes 100% transdermal absorption (as a precise $logP_{ow}$ is unknown, and molecular weight species ~650 Da), a 31 kg child with a skin contact area of ~180 cm^2, a contact time of 1 hour each day for a year (365 days) to PVC (density 1.41 g/cm^3) containing 3.6% (w/w) notified chemical:

$$\text{Dermal exposure (mg/kg/day)} = \frac{A(cm^2) \times T(hr) \times C(mg/cm^3) \times Kp(cm/hr) \times Events/yr}{365\ days/yr \times W(kg)}$$

$$= \frac{180 \times 1 \times 50.8 \times (9.14\times10^{-14}) \times 365}{365 \times 31}$$

$$= 3.09\times10^{-14}\ mg/kg\ bw/day$$

However, since the actual Kp of the notified chemical in solid PVC will be much lower than that in a low viscosity solvent, this dermal absorption value is a gross overestimate. In PVC (and particularly in unplasticised PVC), the probable dermal exposure level is likely to be considerably less than that above, as the diffusion coefficient of the notified chemical is likely to be several orders of magnitude smaller. However, this worst-case estimate will be used for risk assessment purposes, as it will account for situations of higher exposure, such as where higher temperatures may occur (e.g. articles in the Australian summer sun), or where the notified chemical is incorporated into plasticised PVC.

This level of dermal exposure is not considered to be significant for risk assessment purposes.

Oral exposure from potable water
Members of the public may also be exposed to the notified chemical from its migration out of PVC pipes into potable (drinking) water. About 2.5 L of water is needed each day to replace water lost from the body under normal conditions, and this level may be higher where heat and exertion play a role. This intake is reflected in the 1995 Australian National Nutrition Survey (NNS), which sampled the 24-hour food intake of 13,858 Australian respondents aged 2 years and older (McLennan and Podger, 1999). In this survey, the highest mean Australian intake of non-alcoholic beverages (including water) was ~2300 g/person (for respondents in Queensland, although other states showed similar consumption levels during summer months). For children, the mean consumption value was lower (~1200 g/person for age 8-11 years). As this study is a representative sample of the Australian population, these consumption levels are reasonable to estimate the expected daily oral intake of potable water that might contain the notified chemical.

The levels of monomethyl-, dimethyl-, monobutyl- and dibutyltin compounds have been measured in a Canadian study of potable water transported by PVC piping (Sadiki and Williams, 1999). The levels were found

to vary depending on the environmental conditions, but levels for each ranged up to 291, 49.1, 28.5 and 52.3 ng Sn/L, for each organotin, respectively. Of these, the most similar to the notified chemical is considered to be dibutyltin, based on its higher molecular weight and hydrophobicity. Assuming that the concentration and the migration properties of the notified chemical in PVC pipes are similar to dibutyltin, the concentrations of the notified chemical in potable water would be expected to fall in a similar range.

Thus, a probable potable water concentration and probable worst-case daily exposures for adults and children, resulting from the use of the notified chemical in PVC pipes, may be estimated:

Conc. of notified chemical in water	=	0.0000523 mg Sn/L
	=	(0.0000523 × 650 Da (mol wt)) ÷ 118.71 Da (Sn)
	=	2.864×10^{-4} mg/L
Adult oral exposure (70kg)	=	(2.864×10^{-4} mg/L × 2.3 L/day) ÷ 70 kg bw
	=	9.4×10^{-6} mg/kg bw/day
Child (8-11 yr) oral exposure (31kg)	=	(2.864×10^{-4} mg/L × 1.2 L/day) ÷ 31 kg bw
	=	1.1×10^{-5} mg/kg bw/day

* The notified chemical consists of several components of differing molecular weight (MW). An indicative MW of 650 Da has been used in this calculation.

These worst-case exposure estimates may be overestimates, because:

1. The notified chemical (molecular weight > 500 Da) is larger and more hydrophobic than dibutyltin (236 Da), so the true leaching rate and resulting leachate concentrations are likely to be lower than those of dibutyltin;
2. The water solubility of the notified chemical might be very low or negligible (only a limiting water solubility value is available). If it had negligible solubility in water, leaching would not be expected;
3. The leaching of the notified chemical from PVC water piping might be self-limiting and finite in duration. Declining PVC-derived organotin levels in drinking water has been suggested in several studies (Sadiki and Williams, 1999). The phenomenon is variable and not well understood, but it appears that leached organotin levels in drinking water may drop by as much as 100-fold after two weeks to two months of use. Insufficient information is known about these processes to make any quantifying statements.
4. Actual potable water consumption by the Australian population is expected to be lower, due to lower water consumption in cooler climate areas and the consumption of commercial beverages as a significant component of daily fluid intake; and
5. The estimate does not consider the use of household water purification devices, which are popular in many parts of Australia, and which might be expected to remove the notified chemical from water that is ingested.

Additionally, it should be considered that other uniquely Australian environmental considerations (e.g. high summer temperatures) have not been factored into these calculations. The Sadiki and Williams study (Sadiki and Williams, 1999) was conducted on pipes exposed to Canadian environmental conditions, which are expected to be significantly cooler than those observed throughout most of Australia. However, the oral exposure estimate used above is expected to sufficiently account for these differences given the conservative assumptions used.

Another Australian consideration should be the potential for exposure to the notified chemical through the collection of rainwater, particularly in remote and arid areas. The collection of rainwater may involve the use of PVC guttering and water tanks, both of which may be a source for leaching of the notified chemical into the rainwater (although the extent of leaching is likely to be limited, as described above for PVC pipes). Rainwater is commonly used for drinking water, often with only ultra-violet (UV) sterilisation that would not be expected to remove the notified chemical. Other sterilisation methods (e.g. ozone or reverse osmosis) might be expected to degrade or remove the notified chemical. In addition, the acidic pH of rainwater (pH 5-6) would be expected to result in its slow hydrolysis upon storage (eg in rainwater tanks). The hydrolysis products of the notified chemical may be ingested, although volatilisation and loss from rainwater tanks may limit such exposure. Overall, the magnitude of the above exposure estimates is expected to be similar to that of the probable public exposure from rainwater.

Inhalation exposure to the notified chemical from PVC articles
Given the vapour pressure of the notified chemical (and/or its hydrolysis products), its volatilisation from PVC articles should be mentioned as a potential source of public exposure. However, given the proposed exterior and construction uses proposed, inhalation is not expected to be a significant source of exposure to the public. Therefore, the potential for exposure resulting from the use of the notified chemical in the interior of buildings, where vapours may accumulate, has not been assessed.

6.2. Human health effects assessment

The results from toxicological investigations conducted on the notified chemical and some breakdown products/analogues are summarised in the table below. Details of these studies can be found in Appendix B, which also summarises additional toxicological data available on the breakdown products from studies and from international reviews.

A category approach, using monobutyltin trichloride as the main analogue chemical for organotins, is proposed by the notifier. The *in vivo* genotoxicity data, repeated dose oral toxicity, skin sensitisation data, and reprotoxicity data are extrapolated based on the category approach used for organotin stabilisers. The OECD SIDS (Screening Information Dataset) program allows the use of data for the metabolic products of chemicals known to rapidly metabolise or react in the body.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 = 1950 mg/kg bw (female) harmful
Rabbit, acute dermal toxicity	LD50 ≥ 2000 mg/kg bw low toxicity
Rat, acute inhalation toxicity	not available
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Rat, repeat dose <combined> toxicity – 49 days	NOAEL = 15 mg/kg bw/day*
Genotoxicity – bacterial reverse mutation	mutagenic
Inhalation teratology**	no teratogenic effect
In vitro absorption through human and rat epidermis***	human epidermis, up to 0.001% rat epidermis, up to 0.261%

*Based on 2-mercaptoethanol.
**Based on alkyl thiol.
***Based on analogue chemical 1.

Toxicokinetics and metabolism
Some gastric hydrolysis of the notified chemical is likely to occur, to form monobutyltin trichloride, 2-mercaptoethanol and alkyl thiol. Therefore these breakdown products are relevant to the toxicity of the notified chemical. They may also cause toxicity themselves, if formed through decomposition of the notified chemical.

An *in vitro* skin absorption study with analogue chemical 1 demonstrated the potential for skin absorption. There was a low transfer of the notified chemical to the receptor fluid but significant quantities of the chemical were taken into the epidermis. Although organotin compounds are thought to be absorbed through the skin, the molecular weight of both this analogue and the notified chemical is > 500, reducing the potential for absorption. The organotin breakdown product however has a molecular weight < 500.

Acute oral toxicity
The notified chemical is harmful through the oral route, with an apparent lower LD50 in female rats. Based on the estimated LD50 of 1950 mg/kg bw for female rats, the chemical would be classified as harmful by the oral route.

Acute dermal toxicity
In an acute dermal study in rats, there was one death but no systemic effects in surviving animals. Severe local skin effects occurred at the dose sites.

Irritation and sensitisation
The notified chemical is slightly irritating to the skin and eyes of rabbit studies. However severe local effects on the skin (including necrosis followed by eschar formation and exfoliation) were seen in the dermal toxicity study, where longer (24 h) exposure occurred. No data related to skin sensitisation was presented. Concise

International Chemical Assessment Document (CICAD) (2006) notes that studies on irritation and sensitisation of mono- and di-alkyl organotins are highly variable, and that the compounds should be regarded as irritating to skin and eyes and as sensitising. No data was presented on respiratory irritation, however the MSDS for the product containing the notified chemical states that this can occur.

Repeat dose toxicity and developmental toxicity
No studies were conducted using the notified chemical. A number of repeated dose studies using hydrolysed products of the notified chemical were available and some of these were reviewed by international organisations. A worse case No Observed Adverse Effect Level (NOAEL) of 15 mg/kg bw/day was established from a 49-day combined rat toxicity study of 2-mercaptoethanol and has been used for risk characterisation. This study was reviewed in the SIDS Initial Assessment Report (SIAR) for the chemical and is considered reliable. A very low NOAEL (< 1 mg/m^3) for repeat inhalation of monobutyltin trichloride was noted. An inhalation teratology study of the alkyl thiol showed no evidence of teratogenicity.

CICAD (2006) reviewed mono- and disubstituted methyltin, butyltin and octyltin compound and noted that relevant endpoints in short- to medium-term exposures are neurotoxicity, developmental toxicity, immunotoxicity and endocrine disruption, with differences in toxicity across the group of chemicals. Developmental toxicity was not demonstrated in mono-substituted compounds.

Mutagenicity
A literature search of monobutyltin trichloride revealed that it is mutagenic in the Ames Reverse Mutation Assay.

S. typhimurium strains TA98 and TA100 were tested at concentrations of up to 100 μg/plate of monobutyltin trichloride in the absence of metabolic activation. A positive concentration-dependant response was observed in strain TA100 for the test substance. These increases were statistically significant ($p>0.05$) over controls at the respective high concentration level of the test substance. CICAD (2006) found that the majority of *in* vivo studies on mono-alkyl tins are negative. In *in vitro* studies with variable results, there are indications of clastogenicity and effects on spindle formation in mitosis.

Breakdown product toxicity
The breakdown products (monobutyltin trichloride, 2-mercaptoethanol and alkyl thiol) are known to pose hazardous profiles. Some studies on the breakdown products are included in Appendix B. Extraction studies on organotin stabilisers showed that the levels of organotin chlorides decreased rapidly to very low levels within 21 days (summary presented by the notifier).

Effects on health of humans
No adverse effects have been reported during the use of the notified chemical in Australia under the Commercial Evaluation permit.

Based on the available data the notified chemical is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

R22 Harmful if swallowed

Oragnotins in general are known to be irritating to skin and eye and may cause skin sensitisation. The notifier has classified the notified chemical as skin sensitiser.

R43 May cause sensitisation by skin contact

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Based on available information from studies on the notified chemical and its breakdown products, it is considered to be irritant and a sensitiser. Acute oral toxicity is moderate and repeated exposure is expected to have adverse effects. The chemical is potentially mutagenic.

Based on EASE model and a NOAEL of 15 mg/kg bw/day, derived from a 49-day combined rat toxicity study of 2-mercaptoethanol the margin of exposure (MOE) for various activities are as follows:

Activity	*Estimated exposure for notified chemical <mg/kg bw/day>*	*Margin of Exposure*
Manual addition of liquid form	6	2.5
Coupling and decoupling of transfer line	0.6	25

MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Therefore, the risk of systemic effects using modelled worker data may not be acceptable for workers involved in the manual transfer of the notified chemical and connecting of transfer line in the absence of PPE. The risk is considered to be significantly lower with the described use of PPE (gloves, goggles and protective clothing). The fact that the notified chemical is classified as sensitising makes the use of PPE mandatory. Therefore dermal exposure should be well controlled and the risk of systemic effects for workers manually adding the notified chemical to the mixing vessel and connecting the transfer line should be low.

Inhalation exposure to the notified chemical may occur but would be limited by the closed systems and engineering controls in use, including local exhaust ventilation. It is noted that the high processing temperatures in PVC compounding and extrusion of articles will increase volatility of the notified chemical and its breakdown products during these processes. Where inhalation exposure can occur, respiratory protection should also be worn. There is an Australian exposure standard for occupational exposure to organotin compounds of 0.1 mg/m^3 time-weighted average (TWA) as tin, with a short term limit (STEL) of 0.2 mg/m^3 and a note that skin absorption may occur (Central Toxicology Laboratory 2003). This standard would apply to the notified chemical and its tin breakdown products. Inhalation exposure may also occur to 2-mercaptoethanol and alkyl thiol. Control of levels of organotin in air is expected to also reduce levels of the thiol by-products to acceptable levels.

The dermal exposure to the notified chemical migrated from the granulated PVC articles is not considered to be significant for risk assessment purposes given that exposure is likely to be limited and workers have limited instances of handling the grandules.

The risk to workers is considered low provided that integrated controls to reduce both dermal and inhalation exposure are in place.

6.3.2. Public health

Direct exposure of the general public by the dermal route is probable, since the notified chemical may be incorporated into a variety of PVC products that will be available to the general public. The notified chemical is harmful in an acute dermal toxicity study, it is slightly irritating to the skin and eyes and it is a skin sensitiser. However, as the level of dermal exposure to the notified chemical that may result from the handling of PVC articles is expected to be negligible, the expected risk to the public is likewise expected to be very low.

The use of the notified chemical in PVC pipes for potable water may result in oral exposure to members of the public. Using a “worst case” ingestion scenario, low-level exposure is likely, resulting from migration into water from pipes. An oral NOAEL for the notified chemical itself was not available. However, given that the notified chemical is expected to hydrolyse under acidic conditions (such as may occur in the environment or in the stomach after ingestion), it was considered reasonable to use repeated dose toxicity data for its hydrolysis products. A comparison between this toxicological data (for the hydrolysis product with the highest toxicity) and the worst-case oral exposure estimate gives:

Adult:

NOAEL (2-mercaptoethanol)	=	15 mg/kg bw/day (49-day combined rat toxicity study)
Adult oral exposure (70kg)	=	9.4×10^{-6} mg/kg bw/day
Margin of exposure (MOE)	=	1.6×10^6

Child (8-11 yrs):

NOAEL (2-mercaptoethanol)	=	15 mg/kg bw/day (49-day combined rat toxicity study)
Child oral exposure (31kg)	=	1.1×10^{-5} mg/kg bw/day
Margin of exposure (MOE)	=	1.4×10^{6}

Therefore, considering that the "worst-case" oral exposure estimates might be under-representing any actual exposure by a thousand-fold, the margin of exposure would still be greater than 1000. It is worth also considering that this estimate of the public health risk is conservative because:

1. The calculation utilised the repeat dose toxicity of a hydrolysis product with probable higher toxicity than the notified chemical;
2. The exposure estimate was determined using conservative estimates (described above), and that the actual ability of the notified chemical to migrate into potable water is expected to be of short duration (Sadiki and Williams, 1999).

Given the positive mutagenicity test results reported for the notified chemical and the conclusions on the mutagenicity studies of its hydrolysis products, the possibility that the notified chemical has some mutagenic properties cannot be overlooked. It is not possible to quantify any specific risks resulting from the observation of mutagenicity at the present stage of scientific knowledge. However, given that the highest probable exposure is expected to be oral (leading to hydrolysis in the stomach) from potable water, and that some hydrolysis may have occurred in the water prior to ingestion, there is no indication that the notified chemical is likely to pose a significant risk to the public.

Overall, the proposed use of the notified chemical in PVC articles, including its use in pipes intended for potable water, is not expected to present a significant public health risk.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia. Release to the environment during shipping, transport and warehousing will only occur in the unlikely event of accidental spills or leaks of the 200 L steel import drums.

RELEASE OF CHEMICAL FROM USE

The notified chemical is transferred from the import drums to a mixing vessel as part of the preparation of the pre-mix used for the manufacture of fully compounded PVC granules. This transfer is achieved by means of a metering pump. The residual volume in the import drums remaining after this transfer process is approximately 200 mL, which is equivalent to 0.1% of the notified chemical imported annually. The residual notified chemical in the import drums will be decomposed by pyrolysis during drum recycling and the elemental tin produced will be incorporated in the recycled steel. As compounding occurs within dedicated extrusion equipment, no other wastage of the notified chemical is expected to occur. The use of the notified chemical as a thermal stabiliser in the manufacture of compounded PVC is therefore not expected to lead to releases of the chemical to the environment.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical will be combined in the matrix of extruded PVC articles. The ultimate fate of the notified chemical is therefore linked to the disposal of used PVC articles. This is expected to be to landfill where degradation of the polymer matrix may release the notified chemical slowly over time.

7.1.2 Environmental fate

The notified chemical is not readily biodegradable. However, the notified chemical is not expected to be discharged to the aquatic environment in significant quantities based on the intended use and probable disposal pathway. The most likely pathway for release of the notified chemical is in landfill as PVC articles slowly degrade. The notified chemical released by this process is expected to rapidly hydrolyse to soluble tin species or adsorb to soil and organic matter. The soluble tin species are expected to eventually precipitate and form insoluble tin oxides.

For the details of the environmental fate studies please refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

No significant concentrations of the notified chemical are expected in the aquatic environment based on the limited possibility for release and the low water solubility of the notified chemical. The PEC for the notified chemical has therefore not been calculated.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity (96 hours)	LL50 > 200 mg/L[a]	Some toxicity is indicated below the nominal water solubility limit
Daphnia Toxicity (21 days)	NOEL 2.5 mg/L[a]	Toxicity is indicated below the nominal water solubility limit
Algal Toxicity (72 hours)	E_rL50 3.5 mg/L[a]	Toxicity is indicated below the nominal water solubility limit

[a]All concentrations refer to nominal WAF (Water Accommodated Fraction) loading levels.

The ecotoxicology test results indicate that primary producers such as algae are likely to be the most sensitive organisms to the notified chemical.

7.2.1 Predicted No-Effect Concentration

No significant aquatic exposure is anticipated based on the intended use and probable disposal pathway of the notified chemical. Hence, a Predicted No Effect Concentration (PNEC) was not calculated.

7.3. Environmental risk assessment

The notified chemical will not be released in significant quantities to the aquatic environment as it will be compounded into PVC articles. The possibility of significant exposure of aquatic organisms to the notified chemical is therefore low. On this basis, the environmental risk of the notified chemical is considered to be acceptable.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)]. The classification and labelling details are:

R22 Harmful if swallowed
R43 May cause sensitisation by skin contact
S24 Avoid contact with skin
S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S36 Wear suitable protective clothing
S37 Wear suitable gloves

and

As a comparison only, the classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	*Hazard statement*
Acute oral toxicity	4	Harmful if swallowed
Skin sensitisation	1	May cause an allergic skin reaction
Acute hazards to the aquatic environment	2	Toxic to aquatic life based on the ecotoxicity to algae

Human health risk assessment

The notified chemical does not pose an unreasonable risk to workers and the public based on available data and under the proposed conditions of use. Exposure to the notified chemical itself in PVC articles is not likely to be significant but instead hydrolysis products such as oragnotin chlorides are formed.

Environmental risk assessment

The notified chemical is not considered to pose a risk to the environment based on its reported use pattern and the consequent low potential for exposure of aquatic organisms.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following health hazard classification for the notified chemical:
  - R22 Harmful if swallowed
  - R43 May cause sensitisation by skin contact

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - ≥25% R22
  - ≥1% R43

Health Surveillance

- As the notified chemical is a skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of sensitisation.

CONTROL MEASURES

Occupational Health and Safety

- Atmospheric monitoring should be conducted by PVC compounders to measure workplace concentrations in air during use of the notified chemical as an additive in PVC.
  - The exposure standard for Tin, organic compounds (as Sn) is 0.1 mg/m^3 (TWA) and 0.2 mg/m^3 (STEL). A skin notation is included
  - Extruders of PVC articles should consider whether similar workplace monitoring is warranted at their sites

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - Automated chemical transfer apparatus.
  - Local exhaust ventilation

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:

- Procedures designed to minimise spillage during transfer operations together with adequate clean up and disposal.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Gloves, goggles or faceshield and workwear impervious to the notified chemical, and respiratory protection in any situations where inhalation exposure may occur

  Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of to landfill.

Storage

- Store in closed containers in a dry and well-ventilated area.
- The product containing 50% notified chemical should be stored consistent with provisions of State and Territory legislation regarding the Storage of C1 Combustible Liquids.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

Transport and Packaging

- The product containing 50% notified chemical should be transported and packaged consistent with provisions of State and Territory legislation regarding the Storage of C1 Combustible Liquids.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
  - used in consumer products; or
  - additional data available on the migration potential of hydrolysis products; or
  - regulatory action taken on the notified chemical

or

(2) Under Section 64(2) of the Act; if

- the function or use of the chemical has changed from stabiliser (at up to 1%) in granulated PVC to manufacture sewerage pipes, drainage pipes, electrical pipes, potable water pipes and other construction applications (for external use), or is likely to change significantly;
- the amount of chemical being introduced has increased from 200 tonnes per annum, or is likely to increase, significantly;
- if the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

Material Safety Data Sheet
The MSDS of the products containing the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point -18ºC

Method	American Society for Testing and Materials (ASTM) Method No. D 1177.
Remarks	Base on the observations in measuring melting point of notified chemical using OECD TG 102 and because the notified chemical was liquid at room temperature, it was decided a freezing point determination would be more appropriate.
Test Facility	Case Consulting Laboratories, Inc. (1995)

Boiling Point

Method	CCL SOP 10.14 based on the American Society for Testing and Materials (ASTM) Method No. D 1120-89.
Remarks	Due to excessive foaming, no reflux temperature was obtainable. The temperature at which forming was noted was reported.
Test Facility	Case Consulting Laboratories, Inc. (1995)

Vapour Pressure 1.65 kPa at 25ºC

Method	OECD TG 104/ASTM Method No. D 2879.
Remarks	The vapour pressure of the notified chemical at four temperatures in the range 24-78ºC was measured using an isoteniscope. The vapour pressure at 25ºC was interpolated from a plot of the logarithm of measured vapour pressure versus the inverse of temperature.
Test Facility	Case Consulting Laboratories, Inc. (1995)

Water Solubility < 0.3 g/L at 20ºC

Method	Estimated by OECD TG 105 Water Solubility.
Remarks	An upper limit for the water solubility of the notified chemical in de-ionised water at pH 7 and 20ºC was estimated by a method based on the shake-flask technique. Calculated based on the assumption that all of the tin in solution is in the form of the notified chemical.
Test Facility	Case Consulting Laboratories, Inc. (1995)

Hydrolysis as a Function of pH Hydrolysable

Remarks	Attempts to determine the rates of hydrolysis in aqueous solution were confounded by the low water solubility of the notified chemical and the formation of complex and undifferentiated reaction products.
Test Facility	Wildlife International, Ltd. (2007a)

Flammability Upper: 10.4% at 250ºC
Lower: 0.82% at 250ºC

Method	ASTM Method No. E 681.
Test Facility	Chilworth Technology Inc. (2006)

Autoignition Temperature 257-260ºC

Method	ASTM Method No. E 659.
Test Facility	Chilworth Technology Inc. (2006)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Albino CDR Sprague-Dawley derived
- Vehicle: None
- Remarks - Method: Route of administration: oral, via intubation
  Duration of study: A single dose was administered to each animal, followed by 14 days of observations. Range-finding animals were observed for 7 days.
  No postmortem examinations were made on animals used for range finding.

RESULTS

Dose mg/kg bw	*Number and Sex of Animals*	*Mortality*
1200	5 M, 5 F	0
2500	5 M, 5 F	1 M, 4 F
5000	5 M, 5 F	4 M, 5 F

LD50: 1950 mg/kg bw (female)

The acute oral toxicity test exposed albino NZW rats to 1200, 2500 and 5000 mg/kg of notified chemical. Deaths were observed at the 2500 and 5000 mg/kg dose levels. 1 out of 5 males and 4 out of 5 females exposed to the 2500 mg/kg dose level were found dead by day 3, while 4 out of 5 males and 5 out of 5 females at the 5000 mg/kg dose level were found dead by day 6. The LD_{50} for the group is 2500 mg/kg which is indicative of low oral toxicity. Additional calculations, however, suggest that female rats may be more sensitive, with a LD_{50} of only 1950 mg/kg. Most animals exposed to the notified chemical exhibited alopecia of the abdomen, hypoactivity, stained urine and a decrease in food consumption. At elevated doses, wet and dry rales, dry nasal and oral discharge and opacity of the eyes were observed. All but one of the surviving animals (15 out of 16) gained weight throughout the study. Necropsy observations in animals found dead included discoloration of the lung (2 out of 14), stomach (12 out of 14) and intestine (4 out of 14), red fluid in the bladder (1 out of 14) and intestine (6 out of 14), as well as undescended testes found in the body cavity (5 out of 14). Not all of these are likely to be treatment-related findings.

CONCLUSION: The notified chemical was harmful via the oral route.

TEST FACILITY: Bio/dynamics Inc. (1987a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rabbit/Albino New Zealand White
- Vehicle: None
- Type of dressing: Occlusive.
- Remarks - Method: Method analogous to OECD TG 402.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 M, 5 F	2000	1 M

LD50 > 2000 mg/kg bw

Acute dermal toxicity was tested using 5 male albino NZW rabbits. Following a 24 hour exposure to 2000 mg/kg of the notified chemical, one mortality was reported (day 6). Prior to its death, the male animal exhibited faecal staining, hypoactivity and decreased food consumption. All surviving animals exhibited slight body weight loss (or no gain) at day 7; however, weight gain was observed in all animals by day 14. All animals exhibited severe dermal effects at the dose site including necrosis, eschar formation and exfoliation. These effects persisted for the duration of the study. No remarkable observations were made during necropsy.

CONCLUSION The notified chemical was of low acute dermal toxicity. However severe local effects on the skin were observed.

TEST FACILITY Bio/dynamics Inc. (1987b)

B.3. Acute toxicity – inhalation

There were no acute inhalation toxicity test data submitted.

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD USEPA: Acute Exposure, Primary Dermal Irritation.

Species/Strain	Rabbit/Albino New Zealand White
Number of Animals	3 M, 3 F
Vehicle	None
Observation Period	72 hours
Type of Dressing	Occlusive.
Remarks - Method	Method analogous to OECD TG 404

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	1.83	2	72 hours	1
Oedema	0	0	-	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for ALL animals.

The test substance produced mild dermal irritation. All six animals exhibited very slight (barely perceptible) or slight erythema with oedema.
By 72 hours, one animal was free of dermal irritation and the remaining five animals had very slight erythema.

CONCLUSION The notified chemical was slightly irritating to the skin.

TEST FACILITY Bio/dynamics Inc. (1987c)

B.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD USEPA: Acute Exposure, Primary Eye Irritation.

Species/Strain	Rabbit/Albino New Zealand White
Number of Animals	4 M, 2 F
Observation Period	10 days or until no signs of irritation were present.
Remarks - Method	Method analogous to OECD TG 405.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0.83	2	72 hours	0
Conjunctiva: chemosis	0.55	2	48 hours	0
Conjunctiva: discharge	0.22	2	24 hours	0
Corneal opacity	0	+**	48 hours	0
Iridial inflammation	0.17	1	48 hours	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for ALL animals.
** Slight dulling of normal lustre, considered milder than the numerical scores.

The test substance produced mild to moderate ocular irritation. All six animals exhibited mild to moderate conjunctival irritation (redness, chemosis, discharge), three exhibited slight dulling of the corneal surface and/or corneal ulceration and four had iridal damage or changes. Animals were recovered by day 7.

CONCLUSION The notified chemical was slightly irritating to the eye.

TEST FACILITY Bio/dynamics Inc. (1987d)

B.6. Repeat dose toxicity – analogue chemicals

	NOAEL	International Reviews
Monobutyltin trichloride		
Repeated dose studies		
1. 28-day inhalation in rats (1, 10, or 30 mg/m^3)	< 1 mg/m^3	SIAR (2006)*
2. 90-day oral in rats# (19 and 15–25, 96 and 101, 521 and 533 mg/kg bw/day for males and females, respectively	96 and 101 mg/kg bw/day for males and females, respectively	SIAR (2006)*
Developmental toxicity studies		
3. Full gestational study in rats (oral exposure at gestation days 7–17) (0, 50, 100, 200, and 400 mg/kg bw/day)	> 400 mg/kg/day	CICAD (2006)
4. Oral exposure at gestation days 7–8 in rats (0, 1000, 1500, and 2000 mg/kg bw/day)	2000 mg/kg/day	CICAD (2006)
2-Mercaptoethanol		
Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test in rats		
5. 49-day oral in rats # (15, 50 and 75 mg/kg bw/day)	15 mg/kg/d for general toxicity, maternal toxicity, parturition and development of progeny 75 mg/kg/d for male reproductive and fertility toxicity	SIAR (2005)*
Alkyl thiol		
Repeated dose study		
6. 28-day inhalation in rats, mice and dogs# (0.5, 2.0 and 7.0 ppm)	0.5 ppm	Not available

#Studies provided by the notifier; *Indicated as reliable data in SIAR.

The study methods and NOEL/NOAEL are summarised in the above table and brief discussions are as follows:

Studies using monobutyltin trichloride

1. 28-day inhalation rat study (M&T Chemicals 1988)

Deaths of three male rats and one female rat in the high dose group (30 mg/m^3) occurred after 13-15 days of exposure and were considered test substance-related.

Treatment-related clinical signs including mucoid nasal discharge, rales, lacrimation, salivation, rough coat, abdominal distension (males), ano-genital staining, and fur discoloration mainly at 30 mg/m^3. These symptoms were not observed during the recovery period.

Mean body weights decreased during all (males) or part (females) of the 4-week exposure period. Abnormal hematology was reported in all treated animals, increasing in severity at 30 mg/m^3. In the high-exposure group (30 mg/m^3) these included increased mean hemoglobin values (males and females), increased mean erythrocyte counts (males), and increased mean hematocrit values (females). Female rats in all exposure groups exhibited increased mean erythrocyte counts. Differences from controls were slight, though often significant. Hematology results in female rats in the recovery groups were comparable to controls. Male rats in the recovery groups exhibited increased mean erythrocyte counts (high dose group - 2 weeks recovery) and increased hematocrit, hemoglobin, and erythrocyte counts (mid and high dose group - 4 weeks recovery). Gross necropsy observations included increased discoloration and amorphous material in the lungs, alveolar edema (dose-related), peribronchial lymphoid cell accumulation, perivascular lymphoid cell infiltrate, and accumulation of alveolar macrophages.

*2. 90-day rat dietary study of monobutyltin trichloride (*Appel and Waalkens-Berendsen 2004*)*
Treatment-related effects were limited to the high dose group. These included hematological changes (increased reticulocytes in males, decreased mean corpuscular hemoglobin in females, decreased prothrombin time in both sexes, and increased WBC and lymphocytes in males) and clinical chemistry changes (increased ALP, GGT, A/G ratio, bile acids, phospholipids and potassium in males; increased ASAT and triglycerides in both sexes; decreased sodium in males).

3. Full gestational study (Noda et al. 1992)
Wistar rats were treated orally with monobutyltin trichloride (0, 50, 100, 200, and 400 mg/kg body weight per day) during days 7–17 of gestation. Caesarean sections were performed on day 20 of gestation. No maternal toxicity or thymic atrophy was reported, and no dose-dependent developmental toxicity was evident.

4. Partial gestational study (Ema et al. 1995)
Wistar rats were treated with monobutyltin trichloride (0, 1000, 1500, or 2000 mg/kg body weight) via gastric intubation on days 7 and 8 of pregnancy. Maternal deaths were significantly increased at the 1500 and 2000 mg/kg body weight doses, and maternal body weight gain was significantly decreased at the 1000 and 1500 mg/kg body weight doses. However, no external malformations were found in the fetuses. The authors concluded that monobutyltin trichloride is not a developmental toxicant, since effects were seen only at maternally toxic doses.

Study using 2-mercaptoethanol

5. Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test in rats (CIT 2003)
Treatment-related clinical signs include excessive salivation, decreased body weight in males. Systemic effects involved the liver (organ weight increased and vacuolated liver cells in both genders) and the heart (degenerative cardiomyopathy in females at 50 and 75 mg/kg bw/day, and in males at 75 mg/kg bw/day).

No effects were recorded on mating and fertility at 15 mg/kg bw/day. Doses of ≥ 50 mg/kg bw/day, which also induced general toxicity in males and females, prolonged the gestation period and/or affected delivery, with death of pregnant rats. The reproductive effects are not suitable for the differentiation between effects on female fertility and developmental effects.

Study using alkyl thiol

6. Four week subchronic Inhalation Toxicity Study in Rats, Mice and Dogs (International Research and Development Corporation 1985): Animals were exposed to the test substance via inhalation in whole body exposure chambers for 6 hours/day, 5 days/week for 4 consecutive weeks.

Mortality occurred essentially in the high dose mice only. No death occurred in rats and dogs and the treatment-related signs were dry, cracked, peeling of skin which were limited to the high dose animals.

Statistically significant body weight reductions were seen only in high dose male rats. No consistent changes in food consumption in all species were observed.

There were essentially no treatment-related changes in haematology and organ weights in all species. Relevant macroscopic changes were limited to the dogs and rats at high dose, including mainly skin irritation (crusting, cutaneus thickening) and enlargement of superficial lymph nodes (probably as a secondary reaction to the irritation). The most marked microscopic findings were dermal effects (acanthosis, hyperkeratosis and chronic active inflammation with secondary reactive changes in regional lymph nodes) in rats (high dose) and dogs (mid and high dose). Interestingly, there were no clearly treatment-related changes in the mice, except a low incidence of trace levels of centrilobular hepatocellular hypertrophy in high dose mice, therefore, the cause of death of the mice was unknown.

No evidence of respiratory system damage was found in all three species including the mice that died during the study.

The study author did not identify a NOAEL. Based on the available data, a NOAEL is determined to be 0.5 ppm.

B.7.1. Genotoxicity – bacteria – notified chemical

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure and Pre incubation procedure
Species/Strain	*S. typhimurium*: TA98, TA100, TA1535 and TA1537 *E. coli*: WP2 uvrA (pKM101), WP2 (pKM101)
Metabolic Activation System	Aroclor-induced rat liver S9
Concentration Range in Main Test	a) With metabolic activation: 100 - 5000 µg/plate. b) Without metabolic activation: 100 - 5000 µg/plate.
Vehicle	DMSO

RESULTS

The mutagenicity of the notified chemical was tested in the Reverse Mutation Assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvr* and WP2 at concentrations of up to 5000 μg/plate. The initial test was conducted using the plate incorporation method. A positive, concentration-dependant response was observed with strains TA1535 (maximum 7.0 fold increase) and TA1537 (maximum 7.2 fold increase) in the absence of (S-9) metabolic activation. The test protocol stated that a 3-fold increase in revertants over controls for TA1535 and TA1537 were required for the determination of a positive result. Under this criteria, no increase in revertants were seen in these strains in the presence of metabolic activation. However, a concentration-dependant response was observed in strain TA1535 in the presence of metabolic activation with a 2-fold increase in revertants over the control. Although the use of a 3-fold criteria is often used to compensate for historically low baseline revertants seen with these strains, the two-fold rule is still a widely used and accepted criteria for determining mutagenicity. In lieu of the positive dose response observed in TA1535 (maximum 2.5 fold increase), the notified chemical is judged to be mutagenic to TA1535 with metabolic activation. No increase in revertants were observed in any other strain with or without metabolic activation. No evidence of cytotoxicity was noted; slight amount of precipitation was observed at the 3333 and 5000 μg/plate concentration levels.

A second assay was conducted at the same concentration levels using the pre-incubation protocol. No increase in revertants was seen in any strain tested (2-fold or 3-fold), with or without metabolic activation; however, toxicity (based on $\geq$ 50% reduction in the mean number of revertants/plate compared to the mean vehicle control value) was observed at the 5000 μg/plate concentration level. Precipitate was also observed at 333 μg/plate in the presence of metabolic activation and 333 to 3333 μg/plate in the presence of metabolic activation.

CONCLUSION	The notified chemical was mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Microbiological Associates, Inc (1995)

B.7.2. Genotoxicity – analogue chemicals

Monobutyltin trichloride

Analogue tested	Monobutyltin trichloride
Type of study/Route	Micronucleus in vivo/oral
Source	LSR (1991)
Dose tested	10-250 mg/kg bw
Endpoint result/ Conclusion	Not clastogenic
Comments	Toxicological study compliant with OECD guidelines. Statistically significant increase of micronucleated polychromatic erythrocytes with 250 mg/kg bw at 48h but not at 24 or 72h. Dose response could not be evaluated. The increase was in the range for the results with negative controls considered at 24 and 72h. The negative control at 48h was uncharacteristically low.

Summary conclusions of the SIAP (2006) for monobutyltin trichloride

Monobutyltin trichloride was negative in standard Ames assays (*S. typhimurium* strains) conducted with and without metabolic activation and in two *in vitro* assays for chromosomal aberrations conducted with and without metabolic activation, and a Rec-assay conducted without metabolic activation.

Monobutyltin trichloride was positive as a DNA repair SOS inducer and monobutyltin trichloride induced gene mutations in *Salmonella typhimurium* strain TA100, when tested in the absence of metabolic activation.

Monobutyltin trichloride was negative in an *in vivo* mouse micronucleus assay.

B.8 Inhalation teratology

TEST SUBSTANCE Alkyl thiol

Remarks - Method	An inhalation teratology study of alkyl thiol has been conducted in pregnant rats and mice. A single treated group (25 mice and 25 rats) was exposed to 7.4 ppm of alkyl thiol by whole body exposure for 6 hours/day from gestation day 6 through day 16 (mice) or day 19 (rats).
RESULTS	
Remarks - Results	Overt signs of maternal toxicity were observed in the treated animals (including decreased bodyweight gain, ptosis of the eyelids, unkempt haircoat, moribund appearance). All treated mice, and one treated rat, either died, or were killed in extremis. There were no statistically significant differences in the caesarean section observations or the incidence of foetal malformations between the treated rats and the control group. None of the treated mice survived to the end of gestation, so no conclusion can be drawn for the mice.
CONCLUSION	No evidence of teratogenicity was seen in the study
TEST FACILITY	International Research and Development Corporation, (1983)

B.9 In vitro absorption through human and rat epidermis

TEST SUBSTANCE	Analogue chemical 1
METHOD	OECD Draft Guideline 428 (2000) for Dermal Delivery and Percutaneous Absorption: In vitro Method.
CONCLUSION	The proportions of the test substance absorbed through human epidermis and detected in the receptor chamber were 0.0004% and 0.001% (occluded and unoccluded respectively) of dose after 24h exposure, compared to 0.261% and 0.189% thorough rat epidermis. Significantly higher amount, up to 1% in human and up to 10% in rat, was recovered from the epidermal membrane itself. This is a significant percentage of the applied martial that could be bioavailable to the dermis which is not present in this experimental system.
TEST FACILITY	Central Toxicology Laboratory (2003)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.

Inoculum	Activated sewage sludge bacteria
Exposure Period	43 days
Auxiliary Solvent	None
Analytical Monitoring	The total organic carbon in stock solutions, the dissolved organic carbon in test chambers, and the quantity of evolved CO_2 were all determined spectroscopically.
Remarks – Method	The notified chemical and the reference substance (sodium benzoate) were added at nominal levels of 10 mg carbon/L to inoculated mineral salt medium aerated with CO_2-free air.

RESULTS

Test substance		*Reference Substance-Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	0.5	1	0.6
5	1.2	5	48.0
7	3.4	7	66.4
12	12.1	12	85.2
14	15.9	14	89.7
19	27.7	19	101.4
22	33.2	22	100.3
25	36.8	25	101.0
27	41.0	27	102.1
33	46.0	33	102.1
35	49.0	35	102.0
39	52.2	39	101.8
42	55.2	42	101.9
43	56.2	43	101.9

Remarks – Results: The quoted percentages for the degradation of the notified chemical and reference substance are derived in each case from the average of two replicate measurements.

The degradation of the notified chemical was incomplete after 43 days and did not reach the 60% threshold figure over the period of the test. The notified chemical is therefore not readily biodegradable according to the test guidelines.

CONCLUSION: The notified chemical is not readily biodegradable.

TEST FACILITY: Wildlife International, Ltd. (2007b)

C.1.2. Bioaccumulation

Remarks: The notified chemical is expected to have a high log K_{ow} and may therefore have some potential to bioaccumulate. However, this is unlikely to present a hazard to aquatic organisms because the notified chemical is not expected to be released into aquatic environments based on the intended use and probable disposal pathway. Furthermore, the notified chemical is expected to hydrolyse rapidly in water.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD
- Species: Rainbow trout (*Oncorhynchus mykiss*)
- Exposure Period: 96 hours
- Auxiliary Solvent: None
- Water Hardness: 138 mg $CaCO_3$/L
- Analytical Monitoring: Inductively coupled plasma-atomic emission spectrophotometry (ICP-AES) of total tin.
- Remarks – Method: The test solutions were prepared as Water Accommodated Fractions (WAFs) by suspending the notified chemical in filtered well water with stirring for 24 hours. The WAFs for each nominal concentration were decanted from the previously stirred solutions 4 hours before the test chambers were filled.

The concentration of total tin in the WAFs at the beginning of the study and after 4 days in the test chambers was determined by treatment of samples taken mid-depth with 2% v/v concentrated hydrochloric acid. These acidified samples were injected directly into the ICP-AES instrument from which the concentration of total tin in solution was calculated. These measured tin concentrations were used to calculate the concentration of the notified chemical in solution. This calculation was based on the assumption that all tin in aqueous solution was present in the form of the notified chemical.

The test chambers were aerated to maintain the dissolved oxygen concentration above 60% of the air saturation value.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*2.5 h*	*24 h*	*48 h*	*72 h*	*96 h*
19	6.11-0.68	10	0	0	0	0	0
32	1.54-0.48	10	0	0	0	0	0
54	3.00-1.39	10	0	0	0	0	0
90	7.91-3.01	10	0	0	0	0	0
150	14.2-5.57	10	0	0	0	1	1
200	14.7-7.71	10	0	0	0	1	1

- LL50: > 200 mg/L (nominal WAF) at 96 hours.
- NOEL: 90 mg/L (nominal WAF) at 96 hours.
- Remarks – Results: A preliminary non-GLP range finding test found no mortality in the same species of fish after 96 hours at nominal WAF loading rates up to 30 mg/L. At the highest nominal level of 100 mg/L notified chemical, 43% mortality (3 out of 7 fish) was found after 96 hours.

The WAF levels of the notified chemical in the test solutions were typically less than 10% of the nominal values based on the results of the total tin analyses. The levels of notified chemical present in the WAFs after 4 days were typically more than 50% of the initial values, except for the lowest nominal test level (19 mg/L, < 10% of the initial value).

There was less than 50% mortality at all treatment levels. Hence, acute toxicity end-points were not derived. There was some loss of equilibrium for fish at 200 mg/L nominal WAF after 72 and 96 hours, but otherwise

	no sub-lethal effects were observed.
CONCLUSION	The notified chemical shows some toxicity below the level of its nominal water solubility.
TEST FACILITY	Wildlife International, Ltd. (2007c)

C.2.2. Life-cycle toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 211 *Daphnia magna* Reproduction Test – Semi-static
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	None
Water Hardness	140 mg $CaCO_3$/L
Analytical Monitoring	ICP-AES of total tin.
Remarks – Method	The test solutions were prepared as Water Accommodated Fractions (WAFs) by suspending the notified chemical in filtered and sterilised well water with stirring for 24 hours. The WAFs for each nominal concentration were decanted from the previously stirred solutions 4 hours before the test chambers were filled. The test solutions were renewed three times per week. The concentration of total tin in the WAFs was determined by the same method as for the fish toxicity test.

Cumulative survival of parental daphnids and number of offspring released per female daphnid (*Daphnia magna*) after 21 days of exposure to various nominal levels of the notified chemical.

WAF (mg/L)	A	B	C	D	E	F	G	H	I	J	Number of Dead Adult Daphnids	Percent Survival
Total Number of Offspring Released per Daphnid												
Control	199	213	273	224	233	225	163	185	240	251	0	100
0.63	211	218	30	228	214	260	238	243	241	275	1	90
1.3	236	238	221	215	232	237	217	248	267	229	0	100
2.5	191	231	235	215	250	192	224	249	226	211	0	100
5.0	4	223	175	197	0	97	104	244	207	249	3	70
10.0	0	0	0	0	0	0	0	0	0	92	9	10

Nominal loading of notified chemical, daphnid survival and cumulative mean number of offspring released, mean total body length and dry weight of daphnids (*Daphnia magna*)

Test Day 21				
Nominal WAF Loading (mg/L)	Percent Survival	Mean Number of Offspring Released per female (SD)	Mean Total Body Length in mm (SD)	Mean Dry Weight in mg (SD)
Control	100	221 (32.2)	5.7 (0.44)	1.46 (0.27)
0.63	90	236 (21.4)	6.0 (0.24)	1.51 (0.19)
1.3	100	234 (15.5)	5.9 (0.29)	1.45 (0.11)
2.5	100	222 (20.6)	5.9 (0.21)	1.47 (0.22)
5.0	70	200 (49.6)	5.9 (0.21)	1.19 (0.25)
10.0	10	92[a]	5.8[a]	1.40[a]

[a]Insufficient data to calculate a standard deviation.

EL50 (Mortality)	6.2 mg/L (nominal WAF) at 21 days (2.5-10 mg/L, 95% CI)
EL50 (Reproduction)	8.9 mg/L (nominal WAF) at 21 days (7.4-11 mg/L, 95% CI)
NOEL	2.5 mg/L (nominal WAF) at 21 days
LOEL	5.0 mg/L (nominal WAF) at 21 days
Remarks – Results	A preliminary non-GLP range finding toxicity test showed that the notified chemical produced 100% mortality in *Daphnia magna* at nominal WAF loading levels ≥ 9.0 mg/L after 14 days. The level of the notified chemical in the WAFs was typically less than 20% of the nominal loading for each test chamber. The EL50 values quoted above were calculated based on the mortality/immobility and reproduction observed in the first generation daphnids, and the nominal WAF loadings. Reproduction in test chambers containing nominal WAFs loadings of 0.63-5.0 mg/L notified chemical were not statistically different from the negative control based on the results of analysis by the ANOVA method. The reduction in reproduction of the one surviving adult daphnid at a nominal WAF loading of 10 mg/L, although not analysed statistically, was considered to be treatment related. The reduction in growth was statistically significant at a nominal WAF loading of 5.0 mg/L. Hence, the LOEL is 5.0 mg/L (nominal WAF) and the NOEL is 2.5 mg/L (nominal WAF).
CONCLUSION	The notified chemical shows toxicity below the level of its nominal water solubility.
TEST FACILITY	Wildlife International, Ltd. (2007d)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	Freshwater green algae (*Pseudokirchneriella subcapitata*)
Exposure Period	72 hours
Concentration Range	Nominal: 1.6, 2.4, 3.6, 5.3, 8.0 mg/L Actual: 0.15, 0.29, 0.91, 0.89, 0.81 mg/L (WAFs at test initiation)
Auxiliary Solvent	None
Water Hardness	Not measured. The algal growth medium contained 4.4 mg/L

	$CaCl_2$•$2H_2O$ and 15.0 mg/L $NaHCO_3$ which were added to filtered well water of unquantified hardness.
Analytical Monitoring	ICP-AES of total tin.
Remarks – Method	The test solutions were prepared as Water Accommodated Fractions (WAFs) by suspending the notified chemical in algal growth medium with stirring for 24 hours. The clear and colourless WAFs for each nominal concentration were decanted from the previously stirred solutions after settling for 1 hour. The concentration of total tin in the WAFs was determined by the same method as for the fish and daphnia toxicity tests.

RESULTS

Biomass		*Growth*	
E_bL50 *mg/L at 72 h*	*NOE_bC* *mg/L*	*E_rL50* *mg/L at 72 h*	*NOE_rC* *mg/L*
3.2 (nominal WAF) (95% CI: 1.3-8.1 mg/L)	2.4 (nominal WAF)	3.5 (nominal WAF) (95% CI: 3.3-3.6 mg/L)	2.4 (nominal WAF)

Remarks – Results	The calculated concentration of notified chemical in the WAFs reached a limiting value of approximately 0.9 mg/L at test initiation for nominal concentrations ≥ 3.6 mg/L. The concentration after 3 days was typically the same or slightly lower than the initial concentration.
CONCLUSION	The notified chemical shows toxicity below the level of its nominal water solubility.
TEST FACILITY	Wildlife International, Ltd. (2007e)

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