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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

3-Ethyl-2-methyl-2-(3-methylbutyl)-1,3-oxazolidine

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

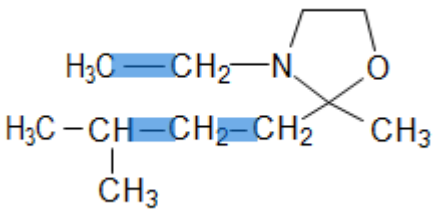
3-Ethyl-2-methyl-2-(3-methylbutyl)-1,3-oxazolidine

1. APPLICANT

International Sales and Marketing Pty Ltd of 262 Highett Road, HIGHETT VIC 3190 has submitted a standard notification statement accompanying their application for an assessment certificate for the chemical 3-ethyl-2-methyl-2-(3-methylbutyl)-1,3-oxazolidine.

2. IDENTITY OF THE CHEMICAL

Chemical name:	3-ethyl-2-methyl-2-(3-methylbutyl)-1,3-oxazolidine
Chemical Abstracts Service (CAS) Registry No.:	143860-04-2
Trade name:	Zoldine MS-Plus
Molecular formula:	$C_{11}H_{23}NO$
Structural formula:	



Molecular weight:	185
Method of detection and determination:	a capillary gas chromatography procedure was provided for determining oxazolidine and impurity content of Zoldine MS-Plus
Spectral data:	ultraviolet/visible (UV/VIS), infrared (IR) and nuclear magnetic resonance (NMR) spectra have been provided for identification of the notified chemical

IR:	the ten strongest bands reported were observed at 2955, 2872, 2801, 1467, 1382, 1255, 1189, 1062, and 855 cm^{-1}
	the bands identified were stated to be consistent with the proposed structure of Zoldine MS-Plus
NMR:	the NMR spectra provided was reported to be consistent with the proposed structure of Zoldine MS-Plus
UV:	no maxima observed below the UV cut-off for the test solvent, methanol (210 nm)

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	clear liquid; slight yellow to yellow colour
Odour:	faint odour
Boiling point:	195.7 to 213.6°C at 983 mbar
Freezing point:	< -25°C
Relative density:	0.87344 at 20°C (mass of 1 m^3 of test substance at 20°C/mass of 1 m^3 of water at 4°C)
Vapour pressure:	60 (+ 5) Pa at 25°C
Water solubility:	not possible to measure as the chemical hydrolyses rapidly
Surface tension:	the surface tensions reported for 0.15% and 0.17% w/v aqueous solutions of the hydrolysis products of Zoldine MS-Plus at 22°C were 69.67 mN/m and 68.4 mN/m, respectively; it was not possible to measure the surface tension of Zoldine MS-Plus due to its rapid hydrolysis in the presence of water
Partition co-efficient (n-octanol/water):	log P_{ow} calculated to be 3.22
Hydrolysis as a function of pH:	not conducted
Adsorption/Desorption:	not conducted
Dissociation constant:	not conducted

Flash point:	69.5°C at 1030 mbar
Flammability:	not flammable, no gas emitted (EEC Method A12: in contact with water/damp air) not flammable, no ignition in air at 20°C (EEC Method A13: solids and liquids)
Combustion products:	complete combustion products are carbon dioxide and water
Decomposition temperature:	not provided
Decomposition products:	not provided
Autoignition temperature:	196°C
Explosive properties:	not explosive when exposed to flame
Reactivity/Stability:	not stated

Comments of physico-chemical properties

The notifier claims that water solubility, hydrolysis, partition coefficient, adsorption/desorption and dissociation data are not applicable to the notified chemical as it hydrolyses in water almost instantly to yield 2-ethylaminoethanol and methyl isoamyl ketone (see further comments under environmental fate below). The partition coefficient, log P (octanol/water), for the compound have been calculated using a method described in the literature (1) and a mean value of 3.22 have been reported. However, this result must be considered as an approximation as pH and rapidly formed more polar hydrolysis products have not been taken into account.

The vapour pressure of the notified substance was determined using the Vapour Pressure Isoteniscope Method in accordance with EEC Directives.

The surface tension was measured with a direct reading surface tension/torsion balance using the harmonised ring method for aqueous solutions containing the hydrolysis products according to OECD guidelines. This is acceptable considering the rapid reaction of the notified chemical with water.

The dissociation constant of the notified chemical becomes that of the amine precursor as the chemical rapidly hydrolyses in water to 2-ethylaminoethanol.

4. PURITY OF THE CHEMICAL

Degree of purity: 90-100% (typically 97%)

Toxic or hazardous impurity/impurities:

Chemical name:	5-methylhexane-2-one
Synomym:	methyl isoamyl ketone
CAS No.:	110-12-3
Weight percentage:	0-5%
Toxic properties:	moderately toxic by oral route (rat acute LD_{50} = 4760 mg/kg; mildly toxic by inhalation and skin contact (2) WSA exposure standard: TWA 234 mg/m^3 (3)
Chemical name:	2-ethylaminoethanol
CAS No.:	110-73-6
Weight percentage:	0-5%
Toxic properties:	moderately toxic by oral route (rat acute LD_{50} = 1170 mg/kg); skin and severe eye irritant (2)

Non-hazardous impurities (> 1% by weight): none

Unknown impurities: a number of unknown impurities are present at < 1%

Additives/Adjuvants: not stated

5. INDUSTRIAL USE

Zoldine MS-Plus will be imported in 55 gallon or 5 gallon pails at an estimated quantity of greater than 1 tonne per annum after the first few years. It will not be manufactured in Australia.

The chemical's proposed use is in high-solids polyurethane coatings as a reactive diluent and water scavenger. The notified chemical will be mixed with paint pigment and the final formulations packaged in a paint factory and transported to end users on demand. The amount of Zoldine MS-Plus to be added to the paint will vary depending on the moisture content present in the pigment and is expected to be a minor component in the final formulation. The polyurethane coatings containing the notified chemical will be used in open hangars at airports as well as in spray booths with filtered extraction systems at industrial sites.

6. OCCUPATIONAL EXPOSURE

The notified chemical will be imported into Australia and transported by road to potential customers (coating manufacturers) within Australia. The coating manufacturers will formulate the chemical into general industrial and aircraft coatings and distribute them to paint applicators. Warehousing will initially be at one location only.

The chemical is classified as a Dangerous Good according to the Australian Dangerous Goods Code (ADG Code) (4) and therefore will be transported and stored in accordance with that code. Transport will be in 'fenced' trucks in 181 kg steel drums with 20 gauge sides or 15.88 kg steel pails with 22 gauge sides. Storage will take place in a Class 8 bonded area within the warehouse facility. Under normal use situations no exposure of transport and storage workers is anticipated.

Manufacturers of general industrial or aircraft coatings will employ approximately 3 workers who will transfer the imported chemical into mixing vessels containing other ingredients. The chemical reacts with moisture in air and is claimed to be relatively expensive. For this reason every attempt will be made to minimise loss of chemical during paint manufacture and packaging. The notified chemical will be transfered directly from the imported containers to the paint/resin vessel via an 'addition station' (an opening into the vessel with a funnel and stop cock). During transfer operations worker exposure will be limited to the time taken to open the drums and attach metering devices. To prevent exposure during this period, exhaust ventilation will be fitted above the 'addition stations' and workers will be required to wear rubber gloves, eye protection and a vapour mask. Once metering devices have been fixed to the drums the potential for worker exposure should be nil.

Each coating applicator will employ approximately 10 workers. The number of coating applicators was not provided. Aircraft will be painted at Sydney and Melbourne airports only. Paint application will be conducted within large open hangars by spray painters wearing full body suits with air makeup hoods. During spray operations, the hangars will be closed and a warning light activated to prevent any other personnel from entering. Industrial coatings will be applied in spray booths with filtered extraction systems. Should personnel be required to work within the booths they will wear full body suit with an air makeup hood.

After paint application the coated surfaces will be cured. During curing all of the Zoldine MS-Plus will react with water (either in the urethane coating or in the air) and no residual chemical will remain in the final dry film of the urethane. At this stage worker exposure will not be possible.

7. PUBLIC EXPOSURE

The notification for Zoldine MS-Plus indicates that it is classified as Class 8 - Corrosive, Packaging Group III and as such will be transported and stored in accordance with the Australian Dangerous Goods Code (4). No public exposure to Zoldine MS-Plus is therefore expected to occur during its storage or distribution.

Zoldine MS-Plus will have applications in the aviation industry and industries involved in the use of general industrial coatings. Aircraft coatings will only be applied in hangars (hangar doors will be closed during spraying) at Sydney and Melbourne airports. Given that the public are usually prohibited from entering hangars, such use is not expected to lead to public exposure. Industrial coatings will be applied in spray booths equipped with filtered extraction systems, therefore such use is not expected to lead to public exposure.

Disposal of Zoldine MS-Plus will be by incineration and expected products of combustion include oxides of nitrogen, carbon dioxide and water. No public exposure to Zoldine MS-Plus is expected to result from its disposal.

The polyurethane coatings will be used in aircraft and general industrial coatings and will not be used to store or package foodstuffs. Although the public may come into contact with polyurethane coatings, no Zoldine MS-Plus is stated to exist in the final urethane coatings, and therefore no public exposure will occur.

8. ENVIRONMENTAL EXPOSURE

Release

Zoldine MS-plus will be stored in a warehouse and transported for International Sales and Marketing Pty Ltd by United Transport Pty Ltd, in accordance with the Australian Dangerous Goods Code. The chemical will be contained in steel drums made for UN specifications. The environmental release of the chemical during transportation is minimal, unless in the case of an accident. Any material which is spilled will be adsorbed on an appropriate substrate and placed in recovery drums for disposal by incineration. The incineration products are mainly carbon dioxide and water, with small amounts of nitrogen oxides.

Another possible release of the chemical will be during the paint manufacture process at the factory. Such operations will take place within the work place by trained workers. A small amount of residue remaining in the used drums will be collected and disposed of by incineration, where it will be pre-mixed with a waste fuel and fed to a gas incinerator or cement kiln.

The chemical will undergo reaction with water present in the pigment. If there is an excess of the chemical in the formulation, it will react with moisture from the atmosphere upon application. Therefore, negligible environmental exposure of the chemical is expected after application.

Fate

The notified chemical belongs to a class of chemicals commonly referred to as Oxazolidines. Oxazolidine-based moisture scavengers have been commonly used in polyurethane coating systems due to their generally good toxicity characteristics and rapid reactivity with water (5). The notified chemical undergoes rapid hydrolysis when exposed to water or moist air to yield 2-ethylaminoethanol and methyl isoamyl ketone. These products then are incorporated into the polymer by cross-linking with the pre-

polymer in the coating. If there is any excess of Zoldine MS-plus in the formulation, it will react with moisture from the atmosphere and the hydrolysis products will eventually evaporate from the coating (methyl isoamyl ketone and 2-ethylaminoethanol have relatively low boiling points of 144°C and 170°C at 760 mm Hg, respectively). Therefore, no Zoldine MS-plus is expected in the final dry urethane coating. Minor amounts may also be contained in waste paint captured by spray booth emissions technology and subsequently landfilled but again this is likely to react with moisture and not persist.

The biodegradability of the notified chemical was assessed by the 'Closed Bottle' method (OECD TG 301D). Sealed bottles containing the test substance (2 mg/L) and inorganic medium were inoculated with activated sewage sludge bacteria and incubated for 28 days. The percentage biodegradation value was calculated by comparing the depletion of dissolved oxygen with the Theoretical Oxygen Demand. The notified chemical attained 43% biodegradation after 28 days. These test results indicate that the chemical may not be readily biodegradable. Additional tests were performed using sodium benzoate as the standard, to determine the inhibitory effect of the chemical. The results indicated that the chemical has no inhibitory effect on bacteria. A second study was also provided for the biodegradation of the notified chemical. The test method used was similar to the OECD TG 301C - 'Modified MITI Test(I)'. Vessels containing the test substance (100 mg/L) were inoculated with activated sludge and incubated for 28 days at 25°C. The percentage biodegradation was determined by measurement of biochemical oxygen demand (BOD), total dissolved organic carbon (TOC), and gas chromatography. According to these methods biodegrability was found to be greater than 90%. No apparent flaws are evident in either of the methods reported. Therefore, it is not possible to draw final conclusions on the biodegradability of the chemical based on the supplied information, though the notified substance and its hydrolysis products are not expected to persist.

9. EVALUATION OF TOXICOLOGICAL DATA

The following studies were provided in accordance with the relevant EEC Directives and complied with Good Laboratory Practice. Genotoxicity studies also followed the appropriate OECD Guidelines.

9.1 Acute Toxicity

Summary of the acute toxicity of Zoldine MS-Plus

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} = 4400 mg/kg (M) = 3000 mg/kg (F)	(6)
acute dermal toxicity	rat	LD_{50} > 2000 mg/kg	(7)
skin irritation	rabbit	corrosive	(8)
skin sensitisation	guinea pig	non-sensitising	(9)

9.1.1 Oral Toxicity (6)

Groups of Sprague-Dawley rats (5/sex) were administered a single gavage dose of Zoldine MS-Plus at 2000 or 3200 mg/kg, and two further groups consisting of 5 female rats or 5 male rats were similarly treated with Zoldine MS-Plus at 2500 and 5000 mg/kg, respectively. Animals were observed for 14 days following treatment. Deaths occurred at 3200 (6/10 rats) and 5000 (3/5 rats) mg/kg from within 4 hours and up to day 8 of dosing. Clinical observations reported up to day 10 included piloerection, hunched posture, increased salivation, pallor, lethargy, decreased respiratory rate, ptosis, abnormal gait and prostration. Gross pathological examination of decedents included congestion of blood vessels in the glandular region of the stomach accompanied by reddening of the wall in the non-glandular region in one male and female at 3200 mg/kg, congestion of blood vessels in the glandular region of the stomach and in the large intestine in two males at 5000 mg/kg, and in the remaining male at 5000 mg/kg the stomach had adhered to the abdominal wall and spleen and several white areas were reported in the glandular region of the stomach.

9.1.2 Dermal Toxicity (7)

Sprague-Dawley rats (5/sex) were dermally (intact skin) exposed to Zoldine MS-Plus (undiluted) at 2000 mg/kg for 24 hours. No deaths or signs of systemic toxicity were observed. Following removal of the dressing, well-defined to moderate erythema and oedema occurred in most rats at the application site. Other signs of dermal irritation included necrosis (4/10 rats), 'stiffening of the treated skin' (1/10 rats), and scabbing and/or desquamation (8/10 rats). Dermal effects were still evident in 7 animals at the end of the 15-day observation period.

9.1.3 Inhalation Toxicity

An acute inhalation toxicity study was not provided on the grounds that the chemical is not volatile and therefore not expected to produce respirable vapour during use. As inhalational exposure during product application is not anticipated when appropriate engineering controls are employed, the omission of this test is acceptable.

9.1.4 Skin Irritation (8)

Three New Zealand White rabbits were dermally (intact skin, semi-occlusive dressing) exposed to 0.5 mL of Zoldine MS-Plus for 4 hours. Necrotic lesions with moderate to severe oedema were observed in all animals on days 1 and 2. Due to the severity of necrotic lesions, one animal was sacrificed on day 2 in order to conduct a histological examination of the treated skin site. Histological examination revealed an extensive area of scab formation and ulceration with loss of epidermis, hair follicles and superficial dermis accompanied by marked oedema with some inflammatory cell infiltration in the deep dermis, panniculus

muscle and sub-panniculus muscle. Due to the severity of necrotic lesions observed on day 4, remaining animals were killed.

9.1.5 Eye Irritation

This study was not undertaken as the substance is corrosive to skin.

9.1.6 Skin Sensitisation (9)

The skin sensitisation potential of Zoldine MS-Plus was studied in guinea pigs using the maximisation test of Magnusson and Kligman (10).

Twenty Dunkin-Hartley guinea pigs were induced by intradermal injections of 0.1 mL of Freund's Complete Adjuvant (FCA) diluted with an equal volume of water for irrigation, 0.1 mL of a 2.5% v/v dilution of the test substance in Alembicol D (a product of coconut oil), and 0.1 mL of a 2.5% v/v dilution of the test substance in a mixture (1:1) of FCA and Alembicol D, followed one week later by topical application of a 20% v/v dilution of the test substance in Alembicol D (maintained under an occlusive dressing) for 48 hours. Fourteen days following the last induction, animals were topically challenged with a 3.5 and 7.5 % v/v dilution of the test substance in Alembicol D (maintained under an occlusive dressing) for 24 hours. A group of 10 control animals were similarly treated however the test substance was omitted.

Necrosis was reported at induction sites of test animals and at injection sites of control animals treated with either FCA in water for irrigation, the test substance in FCA and Alembicol D, or FCA and Alembicol D. As FCA was the only factor common to all treatments, it was concluded that FCA induced the necrosis.
No dermal reactions were reported following challenge treatments in control or treated animals and therefore Zoldine MS-Plus was not considered a skin sensitiser.

9.2 Repeated Dose Toxicity (11)

In a preliminary 7-day dose-ranging study, rats (3/sex/gp) were given Zoldine MS-Plus at 0, 200, 250, 400, 500, 600 or 1000 mg/kg/day in corn oil at dosage volumes of either 2 or 5 mL/kg. All female rats and one male rat given 1000 mg/kg and one female rat given 600 mg/kg were either found dead or killed in extremis. Clinical observations at 1000 mg/kg included hunched posture, unsteady gait, lethargy, loose to liquid faeces, soiled anogenital region, reddish/brown staining around the mouth, and pale and/or gaunt appearance. Salivation was also reported for rats from 250 mg/kg and was suggested to be due to the unpalatability of the test substance. Other effects included reduced bodyweight gains and food consumption from 600 mg/kg, and decreased male liver weights and female spleen weights at 1000 mg/kg. Macroscopic findings at 600 mg/kg in a single female included darkening of the cortex and medulla of the kidneys, congestion of the glandular region of the stomach, congestion and distension of the small and

large intestine and fluid filling the stomach and small intestine, and at 1000 mg/kg findings included yellow fluid in the stomach and intestines, congestion of intestinal blood vessels, and evidence of bleeding in the glandular stomach region. Due to autolysis and cannibalisation, macroscopic examination could not be conducted on 2 females at 1000 mg/kg.

In the main study, Sprague-Dawley rats (5/sex/group) were given Zoldine MS-Plus at 0, 15, 150 or 400 mg/kg as a 20% w/v emulsion in corn oil by oral gavage for 28 days. At 400 mg/kg on day 29, one female rat was found dead; clinical observations reported prior to death were hunched posture and thin appearance. A dose-related decrease in male bodyweights from 150 mg/kg and lower female bodyweights at 400 mg/kg were associated with reduced food and water consumption.

Statistically significant changes in serum biochemical parameters included dose-related increases in ALP and cholesterol from 150 mg/kg and SGPT from 150 mg/kg in females, and at 400 mg/kg, SGPT, urea nitrogen and creatinine were increased in males, SGOT and bilirubin were increased, and albumin and globulin were decreased (associated with lower total protein). In addition, changes in serum electrolytes (increased chloride and decreased phosphorus from 150 mg/kg, and at 400 mg/kg increased sodium (males), and decreased potassium and calcium (females)), were stated to suggest a general electrolyte imbalance. A statistically significant dose-related increase in the total WBC from 15 mg/kg was associated with a dose-related increase in lymphocytes. Other statistically significant changes in haematological parameters occurring from 150 mg/kg were not considered to be of toxicological significance as they were either stated to be within expected ranges, not dose-related or were attributable to individual variation. Although, a low incidence of slight polychromasia and/or anisocytosis occurred (no other information provided), both findings were stated to be common in young laboratory rats.

Organ weight changes included dose-related increases in female and decreases in male liver weights from 150 mg/kg, increased spleen and kidney weights in females at 400 mg/kg, and a dose-related decrease in ovary weights from 150 mg/kg. Gross pathological examinations of rats given 400 mg/kg revealed enlarged livers in two females, roughening and thickening of the epithelial aspect of the forestomach in all males, thickening of the limiting ridge of the forestomach and a pale corpus mucosa of the stomach in all rats (also reported for one female at 150 mg/kg), and pale (and enlarged for two animals) kidneys in all females at 400 mg/kg.

Histopathological examinations revealed effects to the liver, kidney, ovaries, gastrointestinal tract and spleen. Hepatic effects included centrilobular hepatocytic enlargement (often with enlarged nuclei) and centrilobular hepatocytic rarefaction with margination of the cytoplasm in female rats from 150 mg/kg (dose-related increase in incidence and severity) and in males at 400 mg/kg. Renal effects included a dose-related increase in severity of focal degeneration and hyperplasia in the descending part of proximal tubules in all animals from 150 mg/kg (this was reported to be associated with occasional epithelial cells with enlarged nuclei and/or degenerate epithelial cells in the lumen of proximal tubules in a proportion

of affected rats). Ovarian effects included a dose-related increased incidence of partial luteinisation of follicles with occasional degenerate cells in the liquor folliculi of secondary follicles, and reduced numbers of recent corpora lutea from 150 mg/kg, and misshapen (possibly degenerate) oocytes were seen in some primary and secondary ovarian follicles at 400 mg/kg. In the GIT at 400 mg/kg, effects included degenerative and inflammatory changes in the stomach and duodenum (degenerative changes were associated with focal hyperplasia of glandular mucous cells in the stomach and epithelial hyperplasia in the duodenum and jejunum), and hyperplasia and hyperkeratosis at the limiting ridge and/or the non-glandular epithelium of the stomach. Splenic effects occurring in females at 400 mg/kg included increased or decreased cellularity of the white pulp and vascular congestion of the red pulp.

9.3 Genotoxicity

9.3.1 Salmonella typhimurium Reverse Mutation Assay (12)

Salmonella typhimurium TA98, TA100, TA1535, TA1537 and TA1538 were cultured with Zoldine MS-Plus in DMSO at 50, 150, 500, 1500 or 5000 ug/plate with and without metabolic activation using rat liver S-9. All dose levels were plated in duplicate. Vehicle (DMSO) and positive controls were run concurrently. For the positive controls, 2-aminoanthracene was used in the presence of S-9 in all strains and in the absence of S-9, 2-nitrofluorene was used in strains TA98 and TA1538, N-ethyl-N'-nitro-N-nitrosoguanidine in strains TA100 and TA1535, and 9-aminoacridine in strains TA1537. No cytotoxicity was observed in any of the strains treated with Zoldine MS-Plus. No increase in the mutation frequency was reported for any of the treatment or vehicle control groups. The positive controls produced a marked increase in the mutation frequency for all the test strains. Under the condition of the assay, Zoldine was not mutagenic in the *Salmonella typhimurium* reverse mutation assays.

9.3.2 Metaphase chromosome analysis of human lymphocytes cultured in vitro (13)

Cultured human lymphocytes, stimulated to divide by addition of phytohaemagglutinin were exposed to ranges of concentrations of Zoldine MS-Plus in DMSO both in the absence and presence of metabolic activation using rat liver S-9. Cell division of cultured cells was arrested in metaphase after 18 or 32 hours using colchicine. Assays initially conducted allowed for an 18-hour harvest time and were conducted at concentrations of Zoldine MS-Plus ranging from 12.5 to 100 ug/mL in the absence of S-9 and 100 to 800 ug/mL in the presence of S-9. Assays were then conducted allowing for 18-hour and 32-hour harvest times. Concentrations of Zoldine MS-Plus ranged from 50 to 400 ug/mL and 200 to 800 ug/mL for the 18 and 32-hour harvests, respectively in the absence of metabolic activation, and from 100 to 800 ug/mL for the 18 and 32-hour harvests in the presence of metabolic activation. Three hours after treatment, cultures containing the S-9 mix were centrifuged and cell pellets were resuspended in fresh medium and cultured for a further 15 or 29 hours. Duplicate assays were conducted with

ethyl methanesulphonate and cyclophosphamide as the negative and positive controls, respectively.

Treatment of cells with Zoldine MS-Plus did not induce chromosomal aberrations, however, treatment of cells with the positive controls induced significant increases in the proportion of aberrant cells.

9.4 Overall Assessment of Toxicological Data

Based on the toxicity studies provided by the company, Zoldine MS-Plus was of low acute oral and dermal toxicity in rats, it was corrosive to the skin of rabbits and was not a skin sensitiser in guinea pigs. Based on skin effects, the chemical is also expected to be corrosive to the eyes. Repeated administration of Zoldine MS-Plus at 15, 150 or 400 mg/kg/day for 28 days produced a single mortality at the high dose, lower bodyweights, and food and water consumption from 150 mg/kg, and changes indicative of toxic effects to the liver and kidney from 150 mg/kg, ovary and spleen at 400 mg/kg and changes in the gastrointestinal tract consistent with irritation at 400 mg/kg. Zoldine MS-Plus was not mutagenic in *S. typhimurium* using *in vitro* bacterial reverse mutation assays, and did not induce chromosomal aberration in cultured human lymphocytes.

On the basis of submitted data, the notified chemical will be classified as hazardous in accordance with the *Approved Criteria for Classifying Hazardous Substances* (14) in relation to corrosive effects (skin).

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The following studies have been provided.

Summary of the ecotoxicity of Zoldine MS-Plus

Test	*Species*	*Outcome*	*Reference*
acute toxicity	rainbow trout	96h LC_{50} = 129 mg/L NOEL = 20 mg/ L	(15)
acute toxicity	*Daphnia magna*	24h EC_{50} = 60 mg/L 48h EC_{50} = 52 mg/L NOEL = 25 mg/L	(16)
growth inhibition	green algae *Selenastrum capricornutum*	72h E_bC_{50} = 0.99 mg/L E_rC_{50} = 2.90 mg/L NOEL = 0.34 mg/L	(17)
respiratory inhibition	activated sewage sludge bacteria	3h EC_{50} > 100 mg/L	(18)

The concentrations of the test substance in the above studies have been calculated from the measured concentrations of the hydrolysis product, methyl isoamyl ketone. Toxicity is also likely to reflect these species rather than the parent substance.

The acute toxicity of the notified chemical to rainbow trout (*Oncorhynchus mykiss*) was assessed under semi-static conditions in accordance with the OECD guideline for testing of chemicals No. 203. The tests were carried out on groups of seven juvenile fish exposed to a series of concentrations of aqueous solutions of the chemical. The number of dead fish and the incidence of sub-lethal effects after 3, 6, 24, 48, 72, and 96 hours exposure were recorded. The lowest test concentration resulting in 100% mortality and highest test concentration resulting in 0% mortality were found to be 180 mg/L and 92mg/L, respectively. The LC_{50} value of ca. 129 mg/L indicate that the chemical is practically non-toxic to fish. Note however, the relatively low NOEL.

A study was conducted in accordance with OECD guideline for testing of chemicals No. 202, to test the acute toxicity of the notified chemical to *Daphnia magna*. Groups of twenty Daphnia were exposed to 9 different concentrations of the chemical and the incidence of immobilisation was recorded for test and control group at 24 hours and 48 hours. The EC_{50} values of 60 mg/L (24 hours) and 52 mg/L (48 hours) indicate that the chemical is slightly toxic to aquatic invertebrates.

A study was conducted in accordance with OECD guideline for testing of chemicals No. 201 to assess the growth inhibitory effect of the chemical on the unicellular green alga *Selenastrum capricornutum*, Strain No. CCAP 278/4. The median effective concentration for inhibition of growth based on a comparison of areas under the growth curves after 72 hours, E_bC_{50} (72h), was found to be 0.99 mg/L. The median effective concentration for inhibition of growth based on a comparison of maximum growth rates 0 to 72 hours, E_rC_{50} (0-72h), was found to be 2.90 mg/L. These results indicate the the notified chemical is moderately to highly toxic to algae.

The inhibitory effect of the notified chemical on the respiration of activated sewage sludge was assessed by a method in accordance with the OECD guideline for testing of chemicals No. 209. The percent inhibition of respiration was calculated after a 3 hour period by comparing oxygen depletion rates for the test substance with those for the negative control. The satisfactory performance of the method was demonstrated by using a positive control (3,5-dichlorophenol). The EC_{50} (3h) values for respiratory inhibition for the test chemical and 3,5-dichlorophenol (positive control) were found to be >100 mg/L and 28 mg/L, respectively. This indicates that the notified chemical is practically non-toxic to bacteria.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The notified chemical contained in the waste generated during formulation and application of the urethane coatings will be incinerated and landfilled, respectively. The aquatic toxicity studies indicate that the chemical is moderately toxic to algae and slightly toxic to aquatic invertebrates. Therefore, a potential hazard would be likely to result in the rare event of a direct accidental spillage of the chemical into an aquatic compartment. As the product will be shipped in 5-55 gallon pails, the potential massive release will be minimal. The low environmental exposure of the compound as a result of normal use,

rapid hydrolysis, and biodegradability indicates that the notified chemical and its hydrolysis products are unlikely to persist in the environment and the overall environmental hazard should be negligible.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The toxicity profile of the notified chemical suggests the major acute toxicological effects associated with the chemical to be skin corrosion and probable eye corrosion. Cumulative effects are also possible with the target organs being the liver and kidney. The chemical is a non-volatile liquid but reacts with moisture to produce the volatile products 2-ethylethanolamine and methyl isoamyl ketone.
2-Ethylethanolamine is mildly toxic by inhation and skin contact and has an exposure standard of 234 mg/m^3 (3). Methyl isoamyl ketone is a skin and severe eye irritant. The physico-chemical properties of the chemical do not present any additional concerns to workers. The chemical is not flammable and not explosive.

No worker exposure is anticipated during transport and storage. During paint manufacture, workers will handle the chemical for short durations. Skin and eye contact with the notified chemical or the hydrolysis products may occur in the event of spillages, however, exposure will be minimised by the use of gloves and eye protection. Inhalation of the hydrolysis products should be a minor concern under normal use situations as concentrations of these products are expected to be low (short exposure time coupled exhaust ventilation usage). The recommended use of respiratory protection will further reduce the risks to workers by the inhalational route.

During paint application, workers will be required to wear protective equipment suitable for more hazardous ingredients in the urethane coating, such as toluene and isocyanates. The use of this equipment (full body suit with air makeup hood) should reduce exposure by via skin contact, eye contact and inhalation to a safe level.

Public exposure to the notified chemical is not expected to occur.

Under normal use situations the notified chemical should present a low risk to the public and workers.

13. RECOMMENDATIONS

To minimise occupational exposure to Zoldine MS-Plus the following guidelines and precautions should be observed:

- if engineering controls and work practices are insufficient to reduce exposure to Zoldine MS-Plus to a safe level, then personal protective devices which conform to and are used in accordance with Australian Standards (AS) or Australian/New Zealand Standards (AS/NZS) should be worn;

  during spray applications

  chemical protective clothing with an external air supply, intergral gloves and

footwear, conforming to the specifications in AS 3765.1 (19),

during all other handling operations

full face shield selected and fitted in accordance to AS 1336 (20) to comply with AS/NZS 1337 (21),

industrial clothing conforming to the specifications detailed in AS 3765.2 (22),

chemical gloves conforming to AS 2161 (23),

all occupational footwear conforming to AS/NZS 2210 (24);

- the Worksafe exposure standard for 2-Ethylethanolamine: TWA = 234 mg/m^3 (3) should be observed;
- spillage of the notified chemical should be avoided;

  good personal hygiene should be practised to minimise the potential for ingestion;
- a copy of the Material Safety Data Sheet (MSDS) should be easily accessible to employees.

14. MATERIAL SAFETY DATA SHEET

The MSDS for Zoldine MS-Plus was provided in accordance with the *National Code of Practice for the Preparation of a Material Safety Data Sheets* (25).

This MSDS was provided by International Sales and Marketing Pty Ltd as part of their notification statement. The accuracy of this information remains the responsibility of International Sales and Marketing Pty Ltd.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the Act, secondary notification of 3-Ethyl-2-methyl-2-(3-methylbutyl)-1,3-oxazolidine shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise. No other specific conditions are prescribed.

16. REFERENCES

1. A. Leo, C. Hansch, and D. Elkins, *Chem. Reviews*, 1971, 71(6), 525 - 616.

2. Sax N. I. and Lewis R. J. *Dangerous Properties of Industrial Materials*, Van Nostrand Reinhold, New York, 1989.

3. National Occupational Health and Safety Commission, *Exposure Standards for Atmospheric Contaminants in the Occupational Environment.* Australian Government Publishing Service Publ., Canberra, 1995.

4. Federal Office for Road Safety, *Australian Code for the Transport of Dangerous Goods by Road and Rail,* 5th Edition. Australian Government Publishing Service Publ., Canberra, 1992.

5. G.N. Robinson, J.F. Alderman, and T.L. Johnson, *J. Coat. Technol.* 1993, 65(820), 51-55. In *Chemical Abstracts* , 1994,120:166829y.

6. *Zoldine MS-Plus - Acute oral toxicity in rats.* Huntingdon Research Center Ltd, Cambridgeshire, England, 15 February 1993.

7. *Zoldine MS-Plus - Acute dermal toxicity in rats.* Huntingdon Research Center Ltd, Cambridgeshire, England, 11 January 1994.

8. *Zoldine MS-Plus - Skin irritation to the rabbit.* Huntingdon Research Center Ltd, Cambridgeshire, England, 20 January 1993.

9. *Zoldine MS-Plus - Skin sensitisation in the guinea pig.* Huntingdon Research Center Ltd, Cambridgeshire, England, 22 January 1993.

10. Magnusson, B. and Kligman, AM*, Allergic Contact Dermatitis in the Guinea pig: Identification of Contact Allergens*. Thomas C.C., Springfield, Illinois, USA, 1970.

11. *Zoldine MS-Plus - 28-day oral toxicity study (including a 7-day rangefinding study) in the rat.* Huntingdon Research Center Ltd, Cambridgeshire, England, 11 October 1994.

12. *Zoldine MS-Plus - Bacterial mutation assay.* Huntingdon Research Center Ltd, Cambridgeshire, England, 21 January 1993.

13. *Zoldine MS-Plus - Metaphase chromosome analysis of human lymphocytes cultured in vitro.* Huntingdon Research Center Ltd, Cambridgeshire, England, 3 May 1994.

14. National Occupational Health and Safety Commission, *Approved Criteria for Classifying Hazardous Substances.* Australian Government Publishing Service, Canberra, 1994.

15. *Zoldine MS-Plus - Acute Toxicity for Rainbow Trout (Oncorhynchus mykiss).* Huntingdon Research Center Ltd, Cambridgeshire, England, 23 June 1994.

16. *Zoldine MS-Plus - Acute Toxicity to Daphnia magna.* Huntingdon Research Center Ltd, Cambridgeshire, England, 2 July 1993.

17. *Zoldine MS-Plus - Algal Growth Inhibition.* Huntingdon Research Center Ltd, Cambridgeshire, England, 16 August 1994.

18. *Zoldine MS-Plus - Inhibitory Effect on the Respiration of Activated Sewage Sludge.* Huntingdon Research Center Ltd, Cambridgeshire, England, 20 May 1994.

19. Australian Standard 3765.1-1990, *Clothing for Protection against Hazardous Chemicals Part 1 Protection against General or Specific Chemicals* Standards Association of Australia Publ., Sydney, 1990.

20. Australian Standard 1336-1982, *Eye protection in the Industrial Environment.* Standards Association of Australia Publ., Sydney, 1982.

21. Australian/New Zealand Standard 1337-1992, *Eye Protectors for Industrial Applications*, Standards Association of Australia Publ., Sydney, Australia, Standards Association of New Zealand Publ. Wellington, New Zealand, 1992.

22. Australian Standard 3765.2-1990, *Clothing for Protection against Hazardous Chemicals Part 2 Limited protection against specific chemicals.* Standards Association of Australia Publ., Sydney, 1990.

23. Australian Standard 2161-1978, *Industrial Safety Gloves and Mittens (excluding electrical and medical gloves).* Standards Association of Australia Publ., Sydney, 1978.

24. Australian/New Zealand Standard 2210-1994, *Occupational Protective Footwear.* Standards Association of Australia, Standards Association of New Zealand, 1994.

25. National Occupational Health and Safety Commission, 1994, *National Code of Practice for the Preparation of a Material Safety Data Sheets,* Australian Government Publishing Service, Canberra.