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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Oximosilyl perfluoroalkylsulphonamide

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

Oximosilyl perfluoroalkylsulphonamide

1. APPLICANT

Dow Corning Australia Pty Ltd of 21 Tattersall Road, BLACKTOWN NSW 2148 has submitted a standard notification statement in support of their application for an assessment certificate for Oximosilyl perfluoroalkylsulphonamide.

2. IDENTITY OF THE CHEMICAL

The chemical name, molecular and structural formulae, molecular weight and spectral data have been exempted from publication in the Full Public Report and the Summary Report.

Other Name:	Oximosilyl perfluoroalkylsulphonamide
Marketing Name:	DOW CORNING 991 Silicone Hi-Performance Sealant, the product to be imported, contains the notified chemical, Dow Corning 3-0118 Intermediate at 0.3%.
Method of Detection and Determination:	Infra-Red (IR) spectroscopy; ^{13}C Nuclear Magnetic Resonance (^{13}C NMR) spectroscopy; (^{29}Si NMR); Gas Chromatography (GC).
Spectral Data:	IR and NMR spectra were provided.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C & 101.3 kPa:	Amber coloured liquid
Boiling Point:	No well quantified data provided, but the chemical is liquid at 25°C.
Specific Gravity:	1 000 kg/m^3 at 25°C.
Vapour Pressure:	No data provided - see notes below.
Water Solubility:	No data provided - see notes below.

Partition Co-efficient (n-octanol/water):	No data provided - see notes below.
Hydrolysis as a Function of pH:	Hydrolytic breakdown over wide pH range – see notes below.
Adsorption/Desorption:	No data provided - see notes below.
Dissociation Constant:	No data provided - see notes below.
Flash Point:	68°C (closed cup)
Particle Size:	Not relevant as the notified chemical is introduced in a fluid form.
Flammability Limits:	Not determined.
Autoignition Temperature:	Not determined.
Explosive Properties:	Not determined.
Reactivity/Stability:	Reacts with water and moisture

Comments on Physico-Chemical Properties

The chemical is moisture sensitive and the notifier submitted that realistic data on the environmentally significant physico-chemical properties such as water solubility, partition coefficient, adsorption/desorption and dissociation constant would be difficult or impossible to obtain. Although the ASTER (Assessment Tools for the Evaluation of Risk) database of the US EPA was consulted in an attempt to obtain estimates of physico-chemical data calculated on the basis of Quantitative Structure Activity Relationships, no data could be obtained – probably due to the complexity of the molecule.

In the presence of water the notified chemical hydrolyses to a reactive amine and an alkylsilanol. Although no hydrolytic degradation data specific to the notified chemical was given in the dossier, the notifier provided a report (Chandra, 1993) which discussed the hydrolysis of reactive alkoxysilanes as a function of pH and other variables. These materials undergo bond cleavage to an amine or other simple compound and a reactive silanol species, but the half life for this process depends very strongly on the nature of the groups bonded to the silicon atom, and varies over 5 orders of magnitude (0.04 - 340 minutes at 25ºC). The list of substituents provided in the report did not include reactive imido groups such as the – $C(CH_3)$ = N – O – R group which is of relevance for the present compound, and so its hydrolysis half-life is uncertain. Nevertheless, hydrolysis of the imido linkages will produce a perfluorinated organosilane and 2-butylamine. The fluorinated derivative would be expected to have low water solubility, while 2-butylamine is appreciably water soluble.

No data were provided on the n-octanol/water partition coefficient, or on soil adsorption /desorption. However, the perfluorinated moiety would be expected to have very low affinity for water and some affinity for the oil phase. Also, while the fluorinated moiety may have

some affinity for the organic component of soils and sediments there is no information on the strength of binding, and it may be mobile in these media.

4. PURITY OF THE CHEMICAL

Degree of Purity: Approximately 72.9%

Hazardous Impurities:

Chemical name:	2-Butanone, oxime
Synonyms:	Ethyl methyl ketoxime; Ethyl methyl ketone oxime; MEKO
CAS No.:	96-29-7
Weight percentage:	6.2%
Toxic properties:	Xi- R36; R43; R40(3) – see below

Other oxime impurities are present at a concentration of 17.4% and unidentified impurities at 3.5%.

Non-hazardous Impurities (> 1% by weight): None

Additives/Adjuvants: None

5. USE, VOLUME AND FORMULATION

The notified chemical will not be manufactured in Australia, but will be imported as a component, at a concentration of less than 1%, in ready-to-use silicone sealants in which the chemical will act as a cross-linker. The ready-to-use silicone sealant may be repackaged in Australia. A representative sealant: Dow Corning 991 Silicone Hi-Performance Sealant (see attached Material Safety Data Sheet (MSDS)) contains approximately 0.3% of the notified chemical, 4.7% oxime impurities and major components: dimethyl siloxane, hydroxy-terminated (30 – 60%) and calcium carbonate treated with stearic acid (30 – 60%). The projected import volume for the notified chemical is 5 tonnes per year for the first five years.

6. OCCUPATIONAL EXPOSURE

The notified chemical, as a component of a silicone sealant, will be imported in 20 L or 200 L metal drums or tubes for repackaging or in 100 – 500 g polyethylene/polypropylene ready-to-use cartridges and 500 mL foil sausages.

Worker exposure during transport and storage will be limited to accidental spillage.

The notified chemical and silicone sealant are moisture sensitive so the sealant must be repackaged in an air-tight system. Approximately 20 –50 workers are involved in transport

and repackaging for a maximum of 8 hours/day, 5 days/week. The repackaging involves the use of a positive displacement pump equipped with a follower plate. The sealant is pumped under pressure to the cartridges via a flexible hose. The packaging system is airtight but also has a mechanical exhaust system placed over it to remove any escaping vapours. Under these conditions, exposure of workers is unlikely.

The method of application of the silicone sealant was described in the current notification and in a previous submission by the same notifier. The following description is taken from both sources. The notifier estimates that 200 – 500 workers in the building industry may be involved in application of the sealant containing the notified chemical and could be using the sealant 8 hours/day, 5 days/week. The method of use is first to prepare the surface then extrude "beads" of sealant either by hand from the cartridge or by using a compressor operated gun to force beads from the cartridge. Once extruded, the "beads" are spread by means of a spatula or a finger dipped in soapy water (to prevent sticking) although the latter is not recommended with the current product. Dermal exposure to the sealant can, therefore, be frequent. Some secondary exposure of the eyes and mouth may occur by transfer from fingers. Uncured sealant is typically removed using solvents such as white spirit or acetone. Cured material can only be removed with a blade. Most of the work will be conducted on outdoor building sites where vapours are unlikely to accumulate. The Material Safety Data Sheet (MSDS) for the sealant states that methyl ethyl ketoxime is formed on contact with water or humid air although the atmospheric levels are unknown. The notifier stated that goggles, rubber gloves and overalls would be worn during application.

Waste is commonly collected and disposed of to landfill. At this point the sealant should be cured and, although dermal exposure may occur, the notified chemical will not be bioavailable.

7. PUBLIC EXPOSURE

Exposure of the general public as a result of transport and disposal of the product containing the notified chemical is assessed as low. The product containing the notified chemical will be used only in the construction industry, mostly on outdoor building sites where vapours are unlikely to accumulate. Therefore, public exposure during use of the notified chemical is also assessed as low.

8. ENVIRONMENTAL EXPOSURE

Release

The notifier estimates that around 1% of the sealant may be left in the drums after repackaging into the plastic cartridges (ie 2 kg left in every 200 L drum). Assuming 5 tonnes of the (contained) notified chemical are imported each year, this equates to an annual residue of 50 kg. The company stated that other losses associated with repackaging would amount to 10% of the residue quantity – or around 5 kg per annum – leading to total losses associated with repackaging activities of approximately 55 kg per year. If it is assumed that 1 500 tonnes of sealant are imported, and that this is repackaged into 500 g cartridges, an estimated 3 000 000 cartridges containing the notified chemical would be distributed and used

throughout Australia each year.

The notifier indicated that an estimated 1% of the sealant would be left in the cartridges after use, to be disposed of with other solid waste from construction sites, most probably into landfill. This amounts to a maximum annual loss of approximately 50 kg of the notified chemical. However, direct release of the notified chemical is not possible since it is always in contact with other reactive components of the sealant, with which it reacts after exposure to the atmosphere. Some release of the reaction products from the sealant is likely as a consequence of wastage during application, and this would be wiped up with rags or paper towels. Once exposed to the atmosphere the material reacts with water vapour and becomes incorporated into a semi-solid (rubbery) mass. The rags and paper are expected to be disposed of with other waste materials from construction activities.

Fate

The majority of the notified chemical (or more correctly the hydrolytic degradation products) will be incorporated as part of sealant masses in buildings. At the end of their service lives the buildings would be demolished, and it is likely that the sealant masses would be placed into landfill with masonry rubble, or possibly incinerated.

The chemical is not readily biodegradable, and in a CO_2 evolution test (Beck, 1998) conducted with media containing the chemical at a nominal concentration of 20 mg/L, only 5.8% of the theoretical CO_2 had been released after 28 days incubation with sewage sludge bacteria. In contrast 76.1% degradation of the reference compound (sodium benzoate) had occurred after 6 days incubation with the same bacterial culture, and > 90% after 28 days. Fluorinated hydrocarbons have been shown (Remde & Debus, 1996) to be resistant to biodegradation under both aerobic and anaerobic conditions, and abiotic cleavage of C-F bonds is not expected unless assisted by UV radiation. Consequently, this portion of the new chemical is expected to be persistent in the environment.

Although not readily biodegradable, on prolonged exposure to bacterial action, the notified chemical is expected to be substantially mineralised. In a landfill, the sealant mass containing the notified chemical and its breakdown products will slowly degrade as a consequence of microbiological processes with release of gases such as carbon dioxide, methane, ammonia and nitrogen. The silicon content would be transformed to silicate, and the fluorocarbon moiety to volatile low molecular weight compounds, or possibly to fluoride minerals. Incineration will destroy the material with release of water vapour, hydrogen fluoride, oxides of carbon and nitrogen and production of silicates which would become associated with the furnace ash.

Bioaccumulation of the notified chemical itself is of no relevance, since on contact with water it hydrolyses to 2-butylamine and a perfluorinated organosilane as discussed in section 3. The amine has high water solubility and will not bioaccumulate, but the fluorinated by-product is expected to be essentially hydrophobic and may have affinity for fatty tissue.

9. EVALUATION OF TOXICOLOGICAL DATA

Certain toxicology studies have been conducted using the notified chemical and full study reports provided. No acute inhalation, skin sensitisation or repeated dose toxicity studies

with the notified chemical were available. According to the notifier, the notified chemical is hydrolysed to its precursors on contact with moisture. Further hydrolysis releases methyl ethyl ketoxime (MEKO). A number of oxime impurities including MEKO (6.2%) comprise approximately 25% of the notified chemical as synthesised and it is accepted that the skin sensitisation and repeated dose data for MEKO can be used as an indicator of hazard for the notified chemical.

A review of a number of studies on a variety of toxicological endpoints for MEKO was provided (Derelenko, 1997). MEKO is on the NOHSC *List of Designated Hazardous Substances* (National Occupational Health and Safety Commission, 1999a) and is classified as irritant with the risk phrases R36: Irritating to eyes and R43: May cause sensitisation by skin contact.

9.1 Acute Toxicity

Summary of the acute toxicity of Oximosilyl perfluoroalkylsulphonamide, also referred to as DOW CORNING® 3-0118 Intermediate.

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} > 2 000 mg/kg	(Kiplinger, 1994a)
acute dermal toxicity	rat	LD_{50} > 2 000 mg/kg	(Kiplinger, 1995)
skin irritation	rabbit	Slight irritant	(Kiplinger, 1994b)
eye irritation	rabbit	Slight irritant	(Kiplinger, 1994c)
skin sensitisation	guinea pig	Skin sensitiser on the basis of results with MEKO	(cited in Derelenko, 1997)

9.1.1 Oral Toxicity (Kiplinger, 1994a)

Species/strain: Rat/Albino CDF® (F-344)/Crl BR

Number/sex of animals: 5/sex

Observation period: 14 days

Method of administration: A single dose of 1.39 mL (equivalent to 2000 mg/kg bw) of undiluted test substance was administered orally via gastric intubation

Test method: OECD TG 401

Mortality:	None
Clinical observations:	Ataxia was observed in all animals on dosing day. Clear/red ocular discharge, dried red material around the eyes and/or nose and salivation were observed in seven, five and two animals, respectively. One animal was hypoactive and revealed dry/wet yellow urogenital staining. All animals appeared normal by day ten or earlier after dosing except one, which had red ocular discharge on day 13. There were no necropsy findings and no changes were observed in body weights.
LD_{50}:	> 2 000 mg/kg
Result:	the notified chemical was of very low acute oral toxicity in rats

9.1.2 Dermal Toxicity (Kiplinger, 1995)

Species/strain:	Rabbit/New Zealand White
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	A single 1.39 mL (equivalent to 2 000 mg/kg of undiluted test substance) was applied to clipped unabraded dorsal skin under semi-occlusive dressing for 24 hours. Following exposure the dressing was removed and skin wiped with paper towels moistened with tepid tap water to remove residual test substance.
Test method:	OECD TG 402
Mortality:	None
Clinical observations:	All animals appeared normal by day 2 after dosing with the exception of soft stools observed in a female and a male in the first two days and mucoid feces in another male on day 13. No changes or differences were observed in body weights. Necropsy findings included dark red areas in the lungs of one female and accessory splenic tissue in three animals. The latter is a known common congenital abnormality.
Morphological findings:	Very slight to slight erythema was observed in all animals, but no oedema was noted. Desquamation was observed on

two sites.

Signs of skin reactions completely resolved by day 12 or earlier.

Draize scores:

Time after treatment (days)	***Animal #***									
	Males					***Females***				
	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***
Erythema										
1	1[i]	1	2	2	2	2	1	1	1	2
2	1	0	1	0	1	0	0	1	1	1
3	1	0	0	0	1	1	0	1	1	1
Oedema	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0

[i] see attachment 1 for Draize scales

Comment: Erythema was the main skin reaction detected in all animals. In males 1, 3 and 5 very slight erythema (grade 1) persisted up to five, nine and four days, respectively. Very slight erythema persisted up to four days and five days in three (6, 9 and 10) and one (8) females, respectively.

No oedema was observed in any of the animals. Desquamation was observed in one male and one female.

LD_{50}: > 2 000 mg/kg

Result: the notified chemical was of low dermal toxicity in rabbits

9.1.3 Inhalation Toxicity

Data not provided.

9.1.4 Skin Irritation (Kiplinger, 1994b)

Species/strain: Rabbit/New Zealand White

Number/sex of animals: Two males;
One female

Observation period: 7 days

Method of administration: A single 0.5 mL of undiluted test substance was applied to shorn intact area of skin on the back under semi-occlusive dressing for 4 hours, following which the dressing was removed and the skin sites wiped with paper towels moistened with de-ionized water to remove residual test substance.

Test method: OECD TG 404

Draize scores:

Time after treatment (days)	***Animal #***		
	1	***2***	***3***
Erythema			
1 hour	2[a]	1	1
1	1	1	1
2	1	0	1
3	0	0	1
Oedema			
1 hour	0	0	0
1	0	0	0
2	0	0	0
3	0	0	0

[a] see Attachment 1 for Draize scales

Comment: No unscheduled deaths occurred or body weight changes during the study period. Signs of erythema resolved by day 3 following exposure in the two males, and by day 7 in the female. No oedema or other signs of skin irritation were observed in any of the animals.

Result: the notified chemical was slightly irritating to the skin of rabbits

9.1.5 Eye Irritation (Kiplinger, 1994c)

Species/strain: Rabbit/New Zealand White

Number/sex of animals: 3/sex

Observation period: 14 days

Method of administration: Animals were divided into two groups (1 and 2) each consisting of three animals. A single volume of 0.1 mL of undiluted test substance was instilled into the right eye with

the left serving as a control. Thirty seconds after instillation, both eyes (test and control) of the rabbits in group 2 were irrigated with 100 mL of sterile saline for approximately 30 seconds. The eyes of the rabbits in group 1 were unirrigated.

Test method: OECD TG 405

Draize scores of unirrigated eyes:

	Time after instillation																	
Animal	***1 hour***			***1 day***			***2 days***			***3 days***			***4 days***			***7 days***		
Cornea	***o***		***a***	***o***		***a***	***o***		***a***	***o***		***a***	***o***		***a***	***o***		***a***
1	0[1]		-	0		-	0		-	0		-	0		-	0		-
2	0		-	0		-	0		-	0		-	-		-	-		-
3	0		-	0		-	0		-	0		-	0		-	0		-
Iris																		
1	0			0			0			0			0			0		
2	0			0			0			0			-			-		
3	0			0			0			0			0			0		
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	2	1	-	1	0	-	1	0	-	1	0	-	2	1	-	0	0	-
2	1	1	-	1	1	-	1	0	-	0	0	-	-	-	-	-	-	-
3	2	1	-	1	1	-	1	0	-	1	0	-	1	0	-	1	0	-

[1] see Attachment 1 for Draize scales
o = opacity a = area r = redness c = chemosis d = discharge
- = not measured/terminated

Draize scores of irrigated eyes:

	Time after instillation											
Animal	***1 hour***		***1 day***		***2 days***		***3 days***		***4 days***		***7 days***	
Cornea	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***
1	0[1]	-	0	-	0	-	0	-	0	-	0	-
2	0	-	0	-	0	-	0	-	0	-	0	-
3	0	-	0	-	0	-	0	-	0	-	-	-
Iris												
1	0		0		0		0		0		0	
2	0		0		0		0		0		0	
3	0		0		0		0		0		-	

Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	1	1	-	1	0	-	1	0	-	1	0	-	1	0	-	0	0	-
2	1	1	-	1	0	-	1	0	-	1	0	-	1	0	-	0	0	-
3	0	0	-	1	1	-	1	0	-	1	0	-	0	0	-	-	-	-

[1] see Attachment 1 for Draize scales
o = opacity a = area r = redness c = chemosis d = discharge
- = not measured/terminated

Mean scores of unirrigated eyes (24, 48, 72 hours observation):

Animal	***Corneal opacity***	***Iridal inflammation***	***Conjunctival redness***	***Conjunctival chemosis***
1	0	0	1	0
2	0	0	0.6	0.3
3	0	0	1	0.3

Mean scores of irrigated eyes (24, 48, 72 hours observation):

Animal	***Corneal opacity***	***Iridial inflammation***	***Conjunctival redness***	***Conjunctival chemosis***
1	0	0	1	0
2	0	0	1	0
3	0	0	1	0

Comment:

Neither corneal nor iridal inflammation were observed in any of the animals. In the unirrigated eyes, slight to moderate conjunctival inflammation was observed in all animals. Conjunctival inflammation cleared by day seven and 14 in the two males and one female of this group, respectively.

Slight conjunctival inflammation was observed in the eyes

irrigated with saline, which cleared by day 4 and 7 in the female and two males, respectively.

Sodium fluorescein examination revealed no further reactions.

No mortality or body weight changes occurred during the study.

Result: the notified chemical was slightly irritating to the eyes of rabbits.

9.3.2 Skin Sensitisation (cited in (Derelenko, 1997))

MEKO was a strong skin sensitiser in the guinea pig maximisation test in which 8/10 test animals were sensitised. MEKO was a contact sensitiser in a modified Buehler test.

9.2 Repeated Dose Toxicity (Derelenko, 1997)

A number of repeated dose toxicity studies have been conducted on MEKO. These comprise 4-week and 13-week oral, 4-week subcutaneous and 4, 8 and 13-week inhalation toxicity studies.

4-week oral study
Rats were administered MEKO at doses of 250 and 500 mg/kg/day for 28 days. Significant increases in hepatic glutathione occurred at both dose levels at 14 and 28 days concurrently with hepatocellular hypertrophy.

13-week oral study
MEKO was administered to SD rats of both sexes (numbers unknown) by gavage at dose levels of 0, 25, 75 or 225 mg/kg/day, 7 days/week for 13 weeks. No animals died. MEKO induced haemolytic anaemia with compensatory erythropoesis as evidenced by dose-related decreases in red blood cell counts, haemoglobin and haematocrit values accompanied by increased numbers of young red blood cells. In addition, dose-related increases in spleen, liver and kidney weights occurred in all treatment groups, and the spleen and liver exhibited evidence of compensatory red blood cell production. No NOEL was established but the effects at 25 mg/kg/day were minimal.

4-week subcutaneous toxicity
MEKO was administered by subcutaneous injection to groups of six male rats at dose levels of 0.1, 0.5 or 1.0 mL/kg/day, daily for 4 weeks. Transient central nervous system depression occurred immediately following treatment at the two highest doses in addition to a reduction in body weight gain. At 4-weeks, dose-related decreases were seen in red blood cell counts at the two highest doses. Dose-related increases in spleen weight were seen at all three doses.

4-week inhalation toxicity (2 studies)

Groups of rats (10/sex) were exposed to MEKO at concentrations of 0, 60, 283, 533 or 714 ppm, 6 hours/day, 5 days/week for 4 weeks. Mild increases in blood mean corpuscular volume, mean corpuscular haemoglobin, reticulocyte and red blood cell count occurred and spleen weights were elevated at the two top doses. Deposits of iron, thought to be due to red blood cell haemolysis, were found in the spleen at the top dose. The NOEL was 283 ppm. The red blood cell haemolysis observed was consistent with the results of the oral and subcutaneous repeated dose studies.

Another 4-week inhalation study utilised Fischer 344 rats and CD-1 mice exposed to 25, 100 or 400 ppm MEKO, 6 hours/day, 5 days/week for 4 weeks. The significant effects occurred at 400 ppm and were slightly increased methaemoglobin and increased liver and spleen weights in both rats and mice. In rats a slightly decreased erythrocyte count and increased reticulocyte count occurred. Evaluation of the nasal cavity of mice revealed a dose-related focal degeneration of the olfactory epithelium lining the dorsal meatus. Based on this finding, there was no NOAEL in this study. The nasal turbinates of the rats were not evaluated since this effect was not reported in a 90-day study. The NOAEL for haematological effects was 100 ppm in both mice and rats and was 400 ppm, the top dose, for sedative effects.

8-week inhalation study

An 8-week study was performed in rats and mice in which animals were treated with MEKO at 1 000 ppm, 6 hours/day, 5 days/week. One male rat and 2 female mice died during the study. Neurological signs of decreased activity, irregular gait, prostration and lacrimation were observed in the rats. In mice the same effects were less severe. Significant changes in haematology parameters included methaemoglobinaemia, decreases in haemoglobin and haematocrit and increased reticulocytes in both species but to a greater extent in rats. The weights of spleen, liver, adrenals, heart, kidneys and lungs of both species were elevated.

13-week inhalation study

A 13-week study in mice was designed to specifically examine the effects of MEKO on the olfactory epithelium, liver peroxisome proliferation and liver glutathione content in mice. Exposure was by inhalation at levels of 3, 10, 30 or 100 ppm, 6 hours/day. Degeneration of the olfactory epithelium was observed at the end of 1, 2, 4 and 13 weeks. The incidence and severity was greatest at 100 ppm followed by 30 ppm. The degeneration did not appear to be progressive. The NOEL was 3 ppm. Some recovery was observed after 4 weeks following exposure. No enhancement of peroxisome proliferation was observed during the study. Exposure to 30 and 100 ppm produced a significant increase in the levels of hepatic reduced glutathione. It was concluded that reversible damage to the olfactory epithelium of mice is not widespread on exposure to MEKO.

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium and Escherichia coli* Reverse Mutation Assay (San & Wyman, 1994)

Strains:	*S. typhimurium*: TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *E. coli*: WP2*uvr*A
Metabolic activation:	liver fraction (S9 mix) from rats pretreated with Aroclor 1254
Concentration range:	100, 333, 1 000, 3 333, 5 000 μg/plate
Test method:	OECD TG 471- plate incorporation method
Comment:	In a range finding study, a slight precipitate of the test substance was observed at the two highest concentrations used (3 333 and 5 000 μg/plate), but no toxicity was noted. In the main study, slight precipitate was noted at concentrations of 333 μg/plate and higher with no toxicity. In the main study, no increase in the frequency of revertant colonies was observed in any of the bacterial strains, at any concentration, with or without S9 metabolic activation. All positive controls used in the study confirmed the sensitivity of the various strains and the efficacy of the S9-mix. In the absence of S9 the following positive control chemicals were used: 2-nitrofluorene (TA 98, TA 1538); sodium azide (TA 100, TA 1535), 9-aminoacridine (TA 1537) and methyl methanesulfonate (WP2 *uvrA*) and in the presence of S9, 2-aminoanthracene in all strains.
Result:	The notified chemical was not mutagenic under the conditions of the test

9.3.2 Chromosomal Aberration Assay in CHO-K_I Cells (Gudi & Schadly, 1998)

Cells:	Chinese Hamster Ovary (CHO-K_I) Cells
Metabolic activation system:	liver microsomal fraction (S9) from rats pretreated with Aroclor 1254
Dosing schedule:	

Metabolic Activation	• Experiment	Test concentration (μg/mL)	Controls
-S9	1	0, 0.5, 1.5, 5, 15, 50*, 150*, 500* and 1 500*; treatment time = 20 hours	Positive: mitomycin C (0.08 μg/mL)
	2	0, 157, 313, 625*, 1 250*, 2 500* or 5 000*; treatment time = 20 hours 0, 157, 313*, 625*, 1 250*, 2 500*; treatment time = 44 hours	Negative: solvent
+S9	1	0, 0.5, 1.5, 5, 15, 50, 150*, 500*, 1 500* and 5 000*; treatment time = 4 hours; harvest time = 20 hours	Positive: cyclophosphamide (10 μg/mL)
	2	0, 157, 313, 625*, 1 250*, 2 500* or 5 000*; treatment time = 4 hours, harvest time = 20 or 44 hours	Negative: solvent

* cultures selected for metaphase analysis

Test method: Unspecified; similar to OECD TG 473

Comment: The test substance produced a visible precipitate in the treatment medium at dose levels ≥ 1 500 μg/mL in the absence of S9 and at 5 000 μg/mL in its presence.

Result: The notified chemical was non clastogenic under the conditions of the test.

9.3 Carcinogenicity (Derelenko, 1997)

Mice

Mice were exposed to MEKO 6 hours/day, 5 days/week for 18 months at concentrations of 15, 76 or 374 ppm. At terminal sacrifice, no overt signs of systemic toxicity were apparent. A statistically significant increase in incidence of hepatocellular carcinoma occurred in the 374 ppm males. No other effects were observed.

Rats

F-344 rats were exposed to MEKO at concentrations of 15, 75 or 374 ppm, 6 hours/day, 5 days/week for 26 months. Haematology parameters (methaemoglobin, erythrocyte counts) were affected in 374 ppm males and females at 3 month and 12 month sacrifices but not at the 18 month sacrifice. Liver and spleen weights were elevated at 3 months in males and females (and testes weights in the males) exposed to 374 ppm with microscopic effects observed in the spleen. Similar effects occurred at 12 months with microscopic effects in the livers of males. Olfactory degeneration was observed in the dorsal meatus at 75 and 374 ppm which was also observed at 18 months. Other effects at 18 months were elevated weights of testes but not of liver and spleen but microscopic effects in the spleen were still evident at the top exposure level. No induced tumours were seen up to 18 months. However, at terminal sacrifice a statistically significant increase in hepatocellular adenomas and carcinomas was

observed in 374 ppm males (also true for adenomas alone, at 75 ppm). Concentration-related degeneration of olfactory epithelium was observed at terminal sacrifice together with elevated testes weights but no effects of haematology or spleen weights.

9.4 Overall Assessment of Toxicological Data

The notified chemical was of very low acute oral toxicity (LD_{50} > 2 000 mg/kg) and low acute dermal toxicity in rats (LD_{50} > 2 000 mg/kg). It was a slight skin irritant and a slight eye irritant in rabbits. It was not genotoxic *in vitro* as determined by tests for mutagenicity in *Salmonella typhimurium* and clastogenicity in CHO cells.

The notifier supplied a summary of data for skin sensitisation and repeated dose toxicity for MEKO on the basis that it is liberated during use of the product containing the notified chemical and that the product contains approximately 25% oxime impurities.

MEKO is a strong skin sensitiser in guinea pigs.

Repeated dose studies have shown that MEKO has an effect on the nasal epithelium of rodents. However, it was suggested that the differences in nasal anatomy and physiology between rodents and humans make the rodent a poor model for assessing nasal toxicity for water soluble chemicals like MEKO. The NOEL for nasal effects was established as 3 ppm (Derelenko, 1997). Other effects observed were haemolytic anaemia and effects on the nervous system of rats. CNS depression occurs at high levels (NOEL = 714 ppm) (Derelenko, 1997) (see 4-week inhalation toxicity studies in section 9.2). MEKO causes no cumulative or permanent neurological effects.

Effects on the blood are accompanied by compensatory erythropoiesis with tolerance developing on chronic exposure. The lowest NOAEL of 100 ppm has been identified for these effects (Derelenko, 1997).

It was stated in the review of MEKO (Derelenko, 1997) that tumours developed in the liver of male rats in a chronic carcinogenicity study (NOELs: adenomas, 15 ppm; carcinomas, 75 ppm). The tumours appeared late in life and did not affect survival. In mice carcinomas only were induced at a dose level of 374 ppm. It was stated that there have been no human health effects linked to MEKO use in 35 years in commerce with exposure levels up to 2 ppm. The fact that tumours were only induced in male rodents suggests a specific metabolic pathway may be involved. At present the mechanism of induction of liver tumours in male rodents by MEKO is unknown. The rate of oxidation of MEKO to corresponding nitronates or hydroxy nitronates by cytochrome P450 in male rodent microsomes did not correlate with tumour formation (Vokel et al., 1999). Therefore, although there is a possibility that the tumours are specific to rodents, until the mechanism of induction is elucidated, MEKO should be classified as a category 3 carcinogen according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999b) and assigned risk phrase R40(3): Possible risk of irreversible effects. Although MEKO is not currently classified as a category 3 carcinogen in the EU, a proposal to change the current classification has been recently developed by an EU Working Group[1]. Therefore, the notified chemical should also be classified as a category 3 carcinogen and assigned the same

[1] http://www.hse.gov.uk/hthdir/noframes/chip/chip7.htm

risk phrase.

MEKO is on the NOHSC *List of Designated Hazardous Substances* (National Occupational Health and Safety Commission, 1999a) and is classified as irritant with the risk phrases R36: Irritating to eyes and R43: May cause sensitisation by skin contact. Therefore, by default the notified chemical is assigned risk phrase R43.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

Due to the hydrolysis of the compound when exposed to water, no ecotoxicity data were supplied with the notification. The ASTER data base of the US EPA was consulted in respect of estimated toxicity, no results were obtainable, probably because of the complex chemical nature of the compound.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The environmental hazard from the notified chemical appears to be low after it has been used in the intended manner. The chemical is imported as a low percentage (< 1%) component of a finished silicone sealant formulation, and it would only be exposed to the environment as part of a crosslinked polymerised mass with little potential for leaching or escape of fugitive vapours.

It is expected that approximately 55 kg of the chemical will be placed into landfill with residues from repackaging activities, and a further 50 kg in spent sealant cartridges with other construction wastes. At the end of their serviceable lives, structures containing the notified chemical would be demolished and the residues of sealant would most likely be placed into landfill with other rubble. Although the notified chemical is not readily biodegradable, in landfill, the sealant mass containing the notified chemical would undergo slow decomposition to water and gases which may include oxides of carbon and nitrogen, or, under anaerobic conditions, methane and ammonia. The silicon component will ultimately be converted to silicate minerals, and the fluorine to low molecular weight volatile fluorocarbon compounds and fluoride. However, the fluorinated hydrocarbon portion of the molecule is expected to be resistant to both abiotic and biotic degradation, so may persist in the environment.

No ecotoxicity data for the compound was provided in the notification, but very little of the chemical is expected to be released to the water compartment. If the chemical was released to water it would hydrolyse to a complicated fluorinated siloxane species and 2-butylamine. It is possible that the fluorinated species may have potential for bioaccumulation, but since direct release to the water compartment is expected to be small, no potential hazard to the aquatic compartment from use of the notified chemical is envisaged.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Assessment of Toxicological Hazard

The notified chemical was of very low acute oral toxicity (LD_{50} > 2 000 mg/kg) and low

acute dermal toxicity in rats (LD_{50} > 2 000 mg/kg). It was a slight skin irritant and a slight eye irritant in rabbits. It was not genotoxic *in vitro* as determined by tests for mutagenicity in *Salmonella typhimurium* and clastogenicity in CHO cells.

The notifier supplied a summary of data for skin sensitisation and repeated dose toxicity for MEKO on the basis that it is liberated by hydrolysis during use of the product that contains the notified chemical and approximately 4.7% oxime impurities.

MEKO is a strong skin sensitiser in guinea pigs.

Repeated dose studies with MEKO suggested effects on the nasal epithelium, the blood and the central nervous system in rodents. The nasal effects were suggested not to be relevant to humans and high NOELs for the other effects mean that MEKO is not classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999b) for severe effects after repeated or prolonged exposure.

MEKO induced tumours in the livers of male rats but not female rats. The tumours appeared late in life and did not affect survival. The NOEL for adenomas was 15 ppm and for carcinomas, 75 ppm. Hepatocellular carcinomas were also induced in male mice at an exposure level of 374 ppm.

From the toxicological data on MEKO and for the notified chemical, it is classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999b) in terms of skin sensitising effects and is assigned the risk phrase R43: May cause sensitisation by skin contact. MEKO also should be classified as a category 3 carcinogen according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999b) and assigned risk phrase R40(3): Possible risk of irreversible effects. Therefore, the notified chemical also should be classified as a category 3 carcinogen and assigned the same risk phrase. As mentioned above, a proposal to classify MEKO as a category 3 carcinogen has been developed by an EU Working Group.

Assessment of Occupational Health and Safety

The concentration of the notified chemical in the silicone sealant to be imported is below the concentration (1%) at which the sealant would be classified as a skin sensitiser or as a category 3 carcinogen. However, the sealant contains 4.7% oxime impurities as indicated on the MSDS which further states that MEKO is formed upon contact with water or humid air. The sealant, therefore, would be classified as a category 3 carcinogen and a skin sensitiser on the basis of the oxime impurities.

Exposure of workers involved in transport and storage of the imported sealant is expected to be low except in the event of accidental rupture of containers.

Packaging of bulk sealant into cartridges occurs in an airtight system so that the sealant is not exposed to the atmosphere. In addition local exhaust ventilation is employed to capture any fugitive vapours. These controls are essential to ensure that worker exposure during this process is maintained as low as possible, to reduce any consequent risk of adverse health effects.

Workers involved in the application of sealant from cartridges are potentially at risk of skin sensitisation or other irreversible effects. The practice of using a finger dipped in soapy water to spread sealant may lead to workers developing allergic contact dermatitis or other irreversible effects. Product information for Dow Corning 991 Hi-Performance Sealant (for which a MSDS was supplied) specifically states that this should not be done. Therefore, employers should ensure that workers follow the manfacturers instructions to reduce the risk of skin sensitisation.

To minimise the risk of irreversible effects, personal protective equipment must be employed, although respiratory protection should only be required when working in confined spaces. The MSDS recommends self-contained breathing apparatus or supplied air respirator for respiratory protection, safety glasses for eye protection and gloves manufactured from Butyl, Neoprene or Nitrile rubber for skin protection.

Curing of the sealant following its application liberates MEKO fumes. The atmospheric levels are unknown as is the likelihood that the sealant will be used in confined spaces. The only information on the risk of health effects in humans is the statement in the review of MEKO supplied by the notifier (Derelenko, 1997) that levels of MEKO during commercial use have not exceeded 2 ppm and that no adverse health effects in humans have been reported during 35 years of use. The margin of safety for adenomas using this exposure level is 15/2 or 7.5 which is unacceptable. There is no NOHSC exposure standard for MEKO but respiratory protection should be employed to control exposure when working in confined spaces.

The MSDS for the sealant also states that methyl alcohol is liberated by the sealant in contact with water or humid air. Methyl alcohol has a NOHSC exposure standard (TWA, 200 ppm; STEL, 250 ppm) with a skin notation. Therefore, employers must maintain atmospheric levels below these standards.

Public health

Public exposure during transport, disposal and use of the notified chemical is expected to be low given that it is a component of a sealant used only in the construction industry. The risk of health effects in members of the public is therefore low.

13. RECOMMENDATIONS

To minimise occupational exposure to the notified chemical the following guidelines and precautions should be observed:

- Safety goggles should be selected and fitted in accordance with Australian Standard (AS) 1336 (Standards Australia, 1994) to comply with Australian/New Zealand Standard (AS/NZS) 1337 (Standards Australia/Standards New Zealand, 1992); industrial clothing should conform to the specifications detailed in AS 2919 (Standards Australia, 1987); impermeable Butyl, Nitrile or Neoprene rubber gloves should conform to AS/NZS 2161.2 (Standards Australia/Standards New Zealand, 1998); all occupational footwear should conform to AS/NZS 2210 (Standards Australia/Standards New Zealand, 1994a);

- Local exhaust ventilation and good general ventilation should be employed when sealant containing the notified chemical is added to cartridges;

- If sealant containing the notified chemical is used in confined spaces, respiratory protection conforming to AS/NZS 1715 and 1716 (Standards Australia/Standards New Zealand, 1994b; Standards Australia/Standards New Zealand, 1994c) should be used;

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

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

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

14. MATERIAL SAFETY DATA SHEET

The MSDS for a sealant containing the notified chemical was provided in a format consistent with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (National Occupational Health and Safety Commission, 1994).

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

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under subsection 64(1) of the Act, secondary notification of the notified chemical will be required if:

(i) The chemical is to be imported in a formulation at a concentration at or above 1%.

(ii) Any additional testing conducted on MEKO to determine the relevance

to humans of carcinogenesis in male rodents (the MSDS states that such testing is in progress).

Secondary notification of the notified chemical will be required if any of the circumstances stipulated under subsection 64(2) of the Act arise.

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Attachment 1

The Draize Scale (Draize, 1959) for evaluation of skin reactions is as follows:

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

The Draize scale (Draize *et al*., 1944) for evaluation of eye reactions is as follows:

CORNEA

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

CONJUNCTIVAE

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

IRIS

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

Paste text of full public report here