File No: NA/907

May 2001

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Z-44

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Director
Chemicals Notification and Assessment

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1. APPLICANT

Lubrizol International, Inc. (ACN 002 747 944) of 28 River Street, SILVERWATER, NSW 2128 has submitted a standard notification statement in support of their application for an assessment certificate for Z-44.

2. IDENTITY OF THE CHEMICAL

The chemical name, CAS number, molecular and structural formulae, molecular weight, spectral data, details of the polymer composition and details of exact use and import volume have been exempted from publication in the Full Public Report and the Summary Report.

Marketing Name:	Z-44
Molecular Weight:	< 500
Method of Detection and Determination:	Infrared (IR), Ultraviolet (UV) and nuclear magnetic resonance (NMR) spectroscopy.
Spectral Data:	IR, UV and NMR spectra were provided.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C & 101.3 kPa:	Clear, amber, liquid.
Boiling Point:	347°C (with decomposition).
Melting Point:	38 - 45°C
Specific Gravity:	1.03 at 20°C
Vapour Pressure:	< 1.2×10^{-7} kPa at 25°C
Fat Solubility:	Miscible in all proportions
Water Solubility:	0.102 mg/L at 20°C

Partition Co-efficient

(n-octanol/water):	log P_{ow} > 4.06
Hydrolysis as a Function of pH:	At 25°C: $T_{1/2}$ at pH 4.0, > 1 year (estimated) $T_{1/2}$ at pH 7.0, > 1 year (estimated) $T_{1/2}$ at pH 9.0, 28.9 days.
Adsorption/Desorption:	log K_{oc} = 4.23.
Dissociation Constant:	Not applicable.
Flash Point:	167°C
Particle Size:	Not provided.
Flammability Limits:	Not performed.
Autoignition Temperature:	328°C
Explosive Properties:	Not expected to be explosive.
Reactivity/Stability:	Not an oxidiser. The rate of hydrolysis increased with increasing pH. Thermally stable up to 347°C.

3.1 Comments on Physico-Chemical Properties

All tests were performed by Safepharm Laboratories (Safepharm Laboratories Ltd 2000a, 2000b).

The vapour pressure was determined using a vapour pressure balance and Method A4 of Commission Directive 92/69/EEC. Linear regression analysis was used to calculate vapour pressure at 25°C. The low value determined classifies the notified chemical as very slightly volatile.

The water solubility was determined using the column elution method detailed in Method A6 of Commission Directive 92/69/EEC. The notified chemical is classified as being slightly soluble which is consistent with its hydrocarbon structure.

The hydrolytic stability of the notified chemical was determined using Method C7 of Commission Directive 92/69/EEC. The notified chemical has an ester linkage that may undergo hydrolysis under extreme pH. However, the hydrolytic stability tests indicate that the notified chemical is slightly hydrolysed at pH 4 and 7 and moderately hydrolysed at pH 9 at 25°C.

The partition coefficient was determined using the shake-flask method detailed in Method A8 of Commission Directive 92/69/EEC and the estimate provided for the adsorption coefficient, Koc was obtained by the HPLC method detailed in an OECD draft guideline. The slight water solubility is consistent with the high log Pow, indicating a very high affinity for the organic component of soils and sediments. This is confirmed by the high log Koc. The notified chemical is classified as being very hydrophobic and immobile in soil.

Although no dissociation tests were conducted, the notified chemical is unlikely to undergo dissociation in the environmental pH range of 4 to 9. As a hindered phenol, the notified chemical might be expected to be only slightly acidic.

The fat solubility of the notified chemical was determined using OECD TG 116.

4. PURITY OF THE CHEMICAL

Degree of Purity: > 98%

Hazardous Impurities: None.

Non-hazardous Impurities (> 1% by weight): 2% unreacted starting material.

Additives/Adjuvants: None.

5. USE, VOLUME AND FORMULATION

The notified chemical is to be used as a lubricant additive. The notified chemical will be imported into Australia at a level of < 100 tonnes per year for the first five years in a lubricant additive package at a concentration of 2.5 – 8% contained in 205 L steel drums or 1230 L isotainers to be incorporated into engine oils at 0.2 – 1%.

6. OCCUPATIONAL EXPOSURE

As the vapour pressure of the notified chemical is very low, skin contamination would be the main route of occupational exposure. Eye exposure is possible from splashes. Inhalation exposure may occur if oil mist is generated.

Transport and Storage
The notified chemical will be imported into Australia in steel drums. The drums or isotainers would then be transported to customer sites by truck or rail. Exposure to the notified chemical during transport or storage is unlikely except in the case of accidental spillage.

Blending and Packaging
At the blending site, the concentrate product containing the notified chemical will be either decanted from drums or isotainers into a trough from which it is pumped into a blend tank, or pumped directly into the blend tank. It will be formulated into engine oil products by mixing with oil and other additives. The blend facility is a fully automated closed system. The final products resulting from this blending process will contain 0.2 to 1% Z-44. Dermal contamination from residues in pump lines and on drum bungs may occur when workers connect and disconnect the pump lines. If spills and splashes occur, eye exposure is possible. The opportunity exists for exposure when cleaning up spills or leaks and during machine maintenance. The equipment does not require cleaning after each batch as residue is left for next blend. There will be negligible occupational exposure during the fully automatic and

closed blending process.

After blending, the final products containing the notified chemical will be packaged into containers ranging from 1 to 205 litres. The packaging facility is usually located near the blend operation area and equipment is automated. The only opportunity for occupational exposure during packaging would be in the event of broken packages or overflow.

Batch sizes are expected to range from 1 000 to 2 000 kg final product per batch. Each batch will involve 1 to 2 formulators for approximately 3 hours, and 2 to 3 packers for 2 to 5 hours. Blending and packaging facilities are expected to be well ventilated, and all workers will normally wear safety glasses, long sleeved shirts, apron and nitrile or neoprene gloves.

End use
The final products contain up to 1% of the notified chemical. Engine oil lubricants may be used regularly by workers in large and small facilities to top up reservoirs or, less frequently, as a complete lubricant change. Exposure of the hands may be significant as it is uncommon for gloves to be worn during addition of these products to automobiles or machinery.

7. PUBLIC EXPOSURE

Public exposure to the notified chemical during transport and storage should only occur as a result of accidental spillage. Public exposure as a result of lubricant blending from both factory processing and waste disposal should be negligible. Finished lubricant products may be sold to the public who, when changing oil at home, will come into contact via the skin. Some exposure is possible following factory fill and oil change from exhaust emissions and leakage past seals deposited on garage floors. Exposure from these sources should be low.

Ingestion of oil used at home cannot be ruled out, especially by children, although this will be limited by the foul taste of oil products.

8. ENVIRONMENTAL EXPOSURE

8.1 Release

At the customer blending facility losses during the highly automated blending process are not expected. The equipment used will be cleaned with oil and these washings will be used in the formulation of the next batch or another oil blend. In these situations release would occur through accidental spills which would be recycled or collected for incineration. Any of the additive package remaining in the import containers, expected to be less than 1% of the contents, will be washed with mineral oil prior to disposal.

Some minor, diffuse exposure will result from spills during addition of oil to vehicles. However, the greatest potential for exposure is through disposal of wastes containing the additive. A recent survey by the Australian Institute of Petroleum (AIP, 1995) indicates that of the annual sales of automotive engine oils in Australia, some 60% are potentially recoverable (ie not burnt in the engines during use). This report also indicates that around 86% of oil changes take place in specialised automotive service centres, where old oil drained from crankcases could be expected to be disposed of responsibly - either to oil recycling or

incineration. The remaining 14% are removed by "do it yourself" (DIY) enthusiasts, and in these cases some of the used oil would be either incinerated, left at transfer stations where it is again likely to be recycled, or deposited into landfill. However, in a recent survey tracing the fate of used lubricating oil in Australia (Snow, 1997) found that only around 20% of used oil removed by enthusiasts is collected for recycling, approximately 25% is buried or disposed of in landfill, 5% is disposed of into stormwater drains and the remaining 50% is used in treating fence posts, killing grass and weeds or disposed of in other ways. Consequently, assuming that oil removed by professional mechanics is disposed of appropriately (ie burning as workshop heating oil or sent for recycling), negligible release of the notified chemical should result from these professional activities. The DIY proportion of oil changes could potentially lead to improper disposal of used oil at up to 7% of the total import volume, or 7 tonnes of the notified chemical. Most of this is likely to associate with soils or sediments, as will the up to 1 tonne of the notified chemical released to landfill as container residues.

Since the use of the lubricating oils will be occur throughout Australia, all releases resulting from use or disposal of used oil will be very diffuse, and release of the notified material in high concentrations is very unlikely except as a result of transport accidents.

Of the 14% of waste oil produced by DIY enthusiasts, approximately 5% will be disposed to waterways via the stormwater system. This equates to <1% of the total import volume of the notified substance or up to 1 tonne that could be expected to enter the aquatic environment and become associated with sediments.

8.2 Fate

A biodegradation study was conducted using the notified chemical according to OECD TG 301B – Ready Biodegradability; CO_2 Evolution Test (Safepharm Laboratories Ltd, 2000c). Activated sludge, obtained from Severn Trent Water Plc sewage treatment plant in Derbyshire, was mixed with the test substance or standard material (sodium benzoate) at final concentration of 10 mg/L. The biodegradation of sodium benzoate was 71% after 28 days, indicating the test conditions were valid. After 28 days at 21°C, the biodegradation of the test substance was determined to be 6%, which indicates the notified chemical is not readily biodegradable in aerobic environments. According to TG 301B, the substance cannot be considered to be readily biodegradable as it failed to satisfy the 10-day window criterion whereby 60% degradation must be attained within 10 days of the degradation exceeding 10%. However, despite the low apparent rate for biodegradation, material placed into landfill is expected to slowly degrade through the slow biological and abiotic processes operative in these facilities, producing carbon dioxide, methane and water.

The high Koc and Pow values for the notified chemical indicate that it will be immobile in landfill and adsorb onto and associate with the organic component of soils and sediments. Similarly, in the event of accidental release into the water compartment, it is likely to associate with suspended organic material, and eventually be incorporated into sediments.

While the notified chemical meets several of the general characteristics of organic chemicals which exhibit bioaccumulation (Connell, 1990), it has low water solubility (0.0003 mol/m^3) indicative of low bioavailability and hence the material is unlikely to bioaccumulate.

Incineration of waste oil containing the notified chemical would destroy the substance with evolution of water vapour and oxides of carbon. Sludge from waste treatment plants or oil recycling facilities could also be incinerated.

Material containing the notified chemical placed into landfill as a result of irresponsible disposal practices, or from other sources, such as oil treated fence posts would be adsorbed into and associate with soil and eventually slowly degrade as described above.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Summary of the acute toxicity of Z-44

Test	*Species*	*Outcome*	Reference
acute oral toxicity	rat	1. 200 mg/kg < LD_{50} < 2000 mg/kg	(Safepharm Laboratories, 2000d)
		2. LD_{50} > 500 mg/kg	(MB Research Laboratories, 2000)
acute dermal toxicity	rat	LD_{50} > 2000 mg/kg	(Safepharm Laboratories, 2000e)
skin irritation	rabbit	slight to moderate irritant	(Safepharm Laboratories, 2000f)
eye irritation	rabbit	slight irritant	(Safepharm Laboratories, 2000g)
skin sensitisation	guinea pig	1. not sensitising	(Huntingdon Life Sciences 2000)
	guinea pig	2. not sensitising	(Springborn Laboratories, 2000)

9.1.1 Oral Toxicity

9.1.1.1 Acute toxic class method (dosage up to 2000 mg/kg) (Safepharm Laboratories, 2000d)

Species/strain:	rat/ Sprague-Dawley.
Number/sex of animals/dosage levels:	3 females treated at 2000 mg/kg; 3/sex treated at 200 mg/kg.
Observation period:	14 days
Method of administration:	Gavage, using arachis oil as vehicle.

Test method:	OECD TG 423
Mortality:	2/3 animals died at 2000 mg/kg; no mortality at 200 mg/kg.
Clinical observations:	At 2000 mg/kg clinical signs were ataxia, hunched posture, lethargy, pilo-erection, decreased respiratory rate, laboured respiration, splayed gait and staining around the eyes and mouth. No signs were observed at 200 mg/kg.
Morphological findings:	At 2000 mg/kg decedents had haemorrhagic lungs, dark liver, dark kidneys, haemorrhage of the gastric mucosa and haemorrhage of the small intestine. There were no findings for surviving animals killed at the end of the observation period.
Comment:	The LD_{50} was estimated to be in the 500 – 1000 mg/kg range.
LD_{50}:	200 mg/kg < LD_{50} < 2000 mg/kg.
Result:	The notified chemical was estimated to be of moderate to low acute oral toxicity in rats.

9.1.1.2 Dosage of 500 mg/kg (MB Research Laboratories, 2000)

Species/strain:	rat/ Wistar albino.
Number/sex of animals:	5/sex.
Observation period:	14 days
Method of administration:	Gavage (oral), dose 500 mg/kg.
Test method:	OPPTS 870.1100.
Mortality:	No mortality.
Clinical observations:	Diarrhea in one animal 1 hour post-dose.
Morphological findings:	None.
LD_{50}:	> 500 mg/kg.
Result:	The notified chemical was of low acute oral toxicity in rats.

9.1.2 Dermal Toxicity (Safepharm Laboratories, 2000e)

Species/strain:	rat/ Sprague-Dawley.
Number/sex of animals:	5/sex

Observation period: 14 days.

Method of administration: Under semi-occluded gauze dressing for 24 hours, dose 2000 mg/kg.

Test method: OECD TG 402

Mortality: None.

Clinical observations: None.

Morphological findings: None.

Draize scores: All scores zero.

LD_{50}: > 2000 mg/kg.

Result: The notified chemical was of low dermal toxicity in rats.

9.1.3 Inhalation Toxicity

Data not provided.

9.1.4 Skin Irritation (Safepharm Laboratories, 2000f)

Species/strain: rabbit/New Zealand White (NZW).

Number/sex of animals: 3 males.

Observation period: 7 days.

Method of administration: 0.5 mL, single, 4-hour, semi-occluded application.

Test method: OECD TG 404

Draize scores:

Time after treatment (days)	***Animal***		
	1	***2***	***3***
Erythema			
1 hour	1[a]	1	1
1	1	1	2
2	1	1	2
3	0	0	1
7	0	0	0
Oedema			
1	0	0	0
1	0	0	1
2	0	0	1
3	0	0	0
7	0	0	0

[a] see Attachment 1 for Draize scales

Mean Scores (24 – 72 hours)

	1	***2***	***3***
Erythema	0.7	0.7	1.7
Oedema	0	0	0.7

Result: The notified chemical was a slight to moderate irritant to the skin of rabbits.

9.1.5 Eye Irritation (Safepharm Laboratories, 2000g)

Species/strain: rabbit/NZW.

Number/sex of animals: 3 males.

Observation period: 3 days.

Method of administration: 0.1 mL instilled into one eye of each animal.

Test method: OECD TG 405

Draize scores:

Animal	*1 hour*			*1 day*			*2 days*			*3 days*		
Cornea	All scores zero.											
Iris	All scores zero.											
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	1[1]	1	0	0	0	0	0	0	0	0	0	0
2	1	1	1	0	0	0	0	0	0	0	0	0
3	1	1	1	0	0	0	0	0	0	0	0	0

[1] see Attachment 1 for Draize scales
o = opacity a = area r = redness c = chemosis d = discharge

Result: The notified chemical was a slight irritant to the eyes of rabbits.

9.1.6 Skin Sensitisation

9.1.6.1 Magnusson and Kligman Method (Huntingdon Life Sciences 2000)

Species/strain: guinea pig/Dunkin-Hartley.

Number of animals: 20 test/10 control animals.

Induction procedure:

test group:

day 1: Pairs of intradermal injections (0.1 mL) to the scapular region as follows:
- Freund's Complete Adjuvant (FCA), 1:1 in water;
- Z-44, 1% in Alembicol D;
- Z-44, 1% in FCA, 1:1 in Alembicol D.

day 7: Pretreatment of same region with 10% (w/w) sodium lauryl sulphate in petrolatum.

day 8: 100% Z-44 under occlusive patch for 48 hours.

control group: As above with Z-44 omitted.

Challenge procedure:

day 22: Z-44 and Z-44, 50% (v/v) in Alembicol D under occlusive dressing for 24 hours to the flank.

Test method: OECD TG 406

Challenge outcome:

Challenge concentration	• *Test animals* • *Control animals*			
	• *24 hours**	• *48 hours**	• *24 hours*	• *48 hours*
50%	0/20**	0/20	0/10	0/10
100%	0/20	0/20	0/10	0/10

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

Result: The notified chemical was not sensitising to the skin of guinea pigs.

9.1.6.1 Buehler Method (Springborn Laboratories, 2000)

Species/strain: guinea pig/Dunkin-Hartley.

Number of animals: 20 test/10 control animals.

Induction procedure:

test group:
day 0 — 0.3 mL of 100% test substance was placed on a Hilltop chamber backed by adhesive tape (occlusive patch) for 6 hours on the clipped left side of each animal.

day 7, day 14 — As above.

control group: Challenge control.

Challenge procedure:

day 28 — As for induction but to the clipped right side of each animal.

Test method: OECD TG 406

Challenge outcome:

Challenge concentration	• *Test animals* • *Control animals*			
	• *24 hours**	• *48 hours**	• *24 hours*	• *48 hours*
100%	0/20**	0/20	0/10	0/10

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

Result: The notified chemical was not sensitising to the skin of guinea pigs.

9.2 Repeated Dose Toxicity (Safepharm Laboratories, 2000h)

Species/strain: rat/ Sprague-Dawley.

Number/sex of animals: 5/sex/dose group and 5/sex in the three recovery groups.

Dose/Study duration: The notified chemical in Arachis oil was administered for 28 consecutive days at the following concentrations:

dose (mg/kg/day)	group	14-day recovery
0	control	yes
15	low	no
50	intermediate I	no
150	intermediate II	yes
500	high	yes

Method of administration: Gavage (oral).

Test method: OECD TG 407

Bodyweight and Food consumption:
High dose males exhibited a reduced bodyweight gain, reduced dietary intake and slightly reduced food efficiency during weeks 1 and 2 of the study.

Clinical observations:
Clinical signs related to treatment were observed in the high dose group five hours after dosing from day 4. Hunched posture, tiptoe gait, generalised fur loss, increased salivation and red/brown staining of the body surface were observed, more often in females. Signs generally regressed over the second week of treatment. Incidents of ataxia and diuresis were also observed. All observations regressed in the high dose recovery group and no signs were observed from day 36.

Behavioural assessments confirmed the hunched posture and/or tiptoe gait seen in the clinical assessments. No treatment-related observations were recorded for motor activity and forelimb/hindlimb grip strength (functional observations).

An increased startle reflex was observed for high dose males.

Clinical chemistry/Urinalysis/Haematology
Clinical chemistry: High dose males exhibited increased plasma alkaline phosphatase mainly due to one very high value. In high dose females, total protein was elevated and the albumin/globulin (A/G) ratio reduced. The A/G ratio remained lower in the recovery females.

Some chemical chemistry parameters were altered but were concluded to be of no toxicological significance for the following reasons:

- reduced calcium and increased urea in high dose males were within the

historical control ranges;

- reduced inorganic phosphorus in high dose males were not correlated with an effect on a biological system;
- increased chloride in intermediate I females and decreased chloride in high dose females were within the historical control range and were not dose-related;
- reduced glucose only in intermediate II males;
- increased cholesterol in recovery high dose males did not occur in the non-recovery group;
- increased plasma bilirubin in high dose and intermediate II males was within the historical control range with no obvious dose response.

Urinalysis: Increased urine volume was observed in high dose animals and intermediate II dose females.

Haematology: Increased clotting time was observed in intermediate II and high dose males (reversible). Reduced haemoglobin, haematocrit and erythrocyte count were observed in intermediate II and high dose females (reversible).

Some haematology parameters were altered but were concluded to be of no toxicological significance for the following reasons:

- reduced haemoglobin and haematocrit in recovery high dose males were not observed in the non-recovery group;
- reduced haemoglobin, haematocrit and erythrocyte count in low dose females were within the historical control range.

Macroscopic findings:
Enlarged livers were observed in 3 high dose males and 3 high dose females.

Organ weights:
Absolute liver weights were elevated in both male and female animals from the intermediate II and high dose groups; liver weight relative to body weight was elevated in the males in the intermediate I and II and high dose groups and in females in all treated groups.

Some organ weights were altered but were concluded to be of no toxicological significance for the following reasons:

- increased relative kidney weights in high dose males had no histopathological correlate;
- increased relative ovary weight in intermediate II dose females was not observed at the high dose.

Histopathology:
Centrilobular hepatocyte enlargement was observed in both sexes at doses at and above intermediate I. This regressed in recovery group animals. Thyroid follicular hypertrophy with associated depletion of colloid were observed in intermediate II and high dose animals, in intermediate I dose males and possibly in low dose males. Regression was observed in high dose recovery animals.

Comment:
Haematology changes in intermediate II and high dose females were indicative of anaemia but no histopathological changes to the spleen were observed. Extramedullary haemopoiesis observed was stated to be a normal background condition and severities were considered to be within normal limits. In males elevated clotting time was observed in the same dose groups.

The treatment-related changes in clinical chemistry parameters had no histopathological correlates so that a target organ was not identified.

Enlarged livers found in high dose animals correlated with increased liver weights. Increased liver weights were also observed in intermediate II dose animals and in intermediate I dose males. Histopathological analysis revealed centrilobular hepatocyte enlargement in intermediate I, II and high dose animals. All of these observations were suggested to be indicative of an adaptive response in the absence of degenerative or inflammatory changes. It was suggested that the increased incidence of follicular cell hypertrophy with associated depletion of colloid in the thyroid of intermediate II and high dose animals was a secondary response to adaptive changes in the liver.

Result:
The NOAEL for the notified chemical was considered to be 50 mg/kg/day on the basis that effects at 15 and 50 mg/kg/day were confined to minimal adaptive liver and thyroid changes.

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* Reverse Mutation Assay (Safepharm Laboratories, 2000i)

Strains:	*S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100; *Escherichia coli* WP2*uvrA*
Metabolic activation:	Phenobarbitone/ β-naphthoflavone-induced Sprague-Dawley rat liver S9 fraction.
Concentration range:	0, 50, 150, 500, 1500 and 5000 μg/plate
Test method:	OECD TG 471
Comment:	The test substance produced an oily precipitate and opaque film at 5000 μg/plate and was not toxic. Positive controls gave the expected results and negative controls were within historical limits. No significant increases in revertant colonies in any strain at any dose either with or without metabolic activation.
Result:	The notified chemical was non mutagenic under the conditions of the test.

9.3.2 Chromosomal Aberration Assay in Chinese Hamster Lung (CHL) cells (Safepharm Laboratories, 2000j)

Cells: CHL cells.

Metabolic activation system: Phenobarbitone/ β-naphthoflavone-induced Sprague-Dawley rat liver S9 fraction.

Dosing schedule:

• *Metabolic Activation*	• ***Experiment Number***	• *Test concentration (μg/mL)*	• *Controls*
-S9	1	treatment time = 6 hours, harvest time = 24 hours 0*, 1, 2*, 4*, 8*, 12*, 16 μg/mL	Positive: mitomycin C, 0.1 μg/mL Negative: acetone vehicle
	2	treatment time = 24 hours = harvest time 0*, 2, 4*, 8*, 10*, 12, 16 μg/mL treatment time = 48 hours = harvest time 0*, 1, 2, 4*, 8*, 10*, 12 μg/mL	Positive: mitomycin C, 0.05 μg/mL Positive: mitomycin C, 0.025 μg/mL Negative: acetone vehicle
+S9	1	treatment time = 6 hours, harvest time = 24 hours 0*, 105, 210, 420, 840*, 1680*, 2100* μg/mL	Positive: cyclophosphamide, 10 μg/mL Negative: acetone vehicle
	2	treatment time = 6 hours, harvest time = 24 hours 0*, 450, 900, 1800, 2100*, 2400*, 2700* μg/mL	Positive: cyclophosphamide, 10 μg/mL Negative: acetone vehicle

* doses selected for metaphase analysis

Test method:	OECD TG 473
Comment:	The test substance was shown to be toxic and doses were selected accordingly. Statistically significant increases in chromosomal aberrations were not induced either in the presence or absence of metabolic activation.
Result:	The notified chemical was non clastogenic under the conditions of the test

9.3.3 Micronucleus Assay in the Bone Marrow Cells of the Mouse (Safepharm Laboratories, 2000k)

Species/strain:	mouse/ CD-1
Number and sex of animals:	7 males per dose group.
Doses:	0, 375, 750 and 1500 mg/kg.
Method of administration:	Oral (gavage).
Test method:	OECD TG 474
Comment:	The maximum tolerated dose was stated to be 1500 mg/kg. The vehicle control was arachis oil and the positive control was 50 mg/kg cyclophosphamide. Bone marrow samples were taken at 24 and 48 hours after dosing. No statistically significant decrease in PCE/NCE ratio. One premature death in the 1500 mg/kg group at 48 hours and clinical signs indicated systemic absorption of the test substance.
Result:	The notified chemical was non clastogenic under the conditions of the test.

9.4 Overall Assessment of Toxicological Data

The notified chemical was of low acute oral toxicity in rats (500 mg/kg < LD_{50} < 2000 mg/kg) and was of low acute dermal toxicity in rats (LD_{50} > 2000 mg/kg). It was a slight to moderate skin irritant and a slight eye irritant in rabbits. It was not mutagenic in bacteria and was not clastogenic in CHL cells (chromosome aberration assay) or mouse bone marrow cells (micronucleus assay). In a 4-week oral repeated dose study organ toxicity was ascribed to adaptive effects in the liver with associated thyroid follicular hypertrophy. At doses above 50 mg/kg/day, haematology effects were observed. The NOAEL was considered to be 50 mg/kg/day.

The notified chemical is determined to be a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999a) with respect to acute oral toxicity and risk phrase R22: Harmful if swallowed, is assigned.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

Test	*Species*	*Results*
Acute Toxicity	Rainbow Trout *Oncorhynchus mykiss*	LLR_{50} (96 h) = 1500 mg/L WAF** NOEC* (96 h) = 560 mg/L WAF
Acute Immobilisation	Water Flea *Daphnia magna*	ELR_{50} (48 h) = 110 mg/L WAF NOEC (48 h) = 56 mg/L WAF
Chronic exposure/reproduction	Water Flea *Daphnia magna*	ECR_{50} (21 d) = 20 mg/L WAF NOEC (21 d) = 10 mg/L WAF
Growth Inhibition [OECD 201]	Algae *Scenedesmus subspicatus*	ELR_{50} (96 h) > 1000 mg/L WAF NOEC (96 h) >1000 mg/L WAF

* NOEC - no observable effect concentration; ** Water Accommodated Fraction

Full test reports on the ecotoxicity studies for Z-44 were provided by the notifier.

The ecotoxicity tests were performed on the WAF of the notified chemical. The WAF was prepared by adding the required amount of Z-44 to water and the resulting solution was stirred for 23 hours. The mixture was then allowed to stand for 1 hour prior to the removal of undissolved test material by filtration.

The tests on fish (Safepharm Laboratories Ltd, 2000m) were performed using a semi-static methodology in which test preparations were renewed daily to ensure that concentrations of test material were maintained near nominal and to prevent the accumulation of nitrogenous wastes. Observations were performed at 3, 6, 24, 48, 72 and 96 hours. The test was performed using ten specimen fish per loading rate at 14ºC. The tests were conducted using a WAF of the test substance made up at nominal concentrations of 180, 320, 560, 1000 and 1800 mg/L. Analysis of the WAF after 96 hours showed measured concentrations to range from 0.156 – 1.10 mg/L. The results of the definitive study showed that no mortalities or sublethal effects were observed in the test vessels with less than 560 mg/L filtered WAF. No mortalities were observed in the test vessels with less than 1000 mg/L filtered WAF though fish lost equilibrium and swam at the bottom of the test vessel. After 96 hours, 70% mortality was observed at a test concentration of 1800 mg/L filtered WAF. The 96-hour LL_{50} for the notified chemical to *Oncorhynchus mykiss* is 1500 mg/L. However, based on measured concentrations this would appear to be around 1 mg/L.

The immobilisation tests with daphnia (Safepharm Laboratories Ltd, 2000n) were performed under semi-static conditions with observations performed at 24 and 48 hours. The test was performed in duplicate using 10 daphnids per flask at 21ºC. The tests were conducted using a WAF of the test substance made up at nominal concentrations of 10, 18, 32, 56, 100, 180, 320, 560 and 1000 mg/L. Analysis of the WAF after 48 hours showed measured concentrations to range from 0.0383 to 0.966 mg/L. After 48 hours, no immobilised daphnids were observed in the test vessels with less than 56 mg/L filtered WAF and 100% mortality was observed after 48 hours at test concentrations above 180 mg/L filtered WAF. The 48-hour EL_{50} for the notified chemical to *Daphnia magna* is 110 mg/L. However, again based on measured concentrations this would appear to be < 1 mg/L.

The reproduction tests with daphnia (Safepharm Laboratories Ltd 2000o) were performed under semi-static conditions for a period of 21 days. The test was performed on 10 replicates using 1 daphnid per flask at 21ºC. The tests were conducted using a WAF of the test substance made up at nominal concentrations of 10, 18, 32, 56, 100, 180, 320, 560 and 1000 mg/L. Analysis of the WAF after 14 days showed measured concentrations to range from 0.0315 to 0.134 mg/L. After 21 days, there was no immobilisation in either the adult or young daphnid populations in concentrations of the notified chemical of below 10 mg/L filtered WAF. There was 100% immobilisation observed in the adult daphnid population after day 14 in the 32 mg/L filtered WAF group. Therefore, the notified chemical does not impair the reproduction of daphnids that survive until day 21. The 21-day EL_{50} for the notified chemical to *Daphnia magna* is 20 mg/L, but around 0.1 mg/L based on measured concentrations.

Algae were exposed to the test substance at a concentration of 1000 mg/L for 96 h at 24˚C under constant illumination and shaking (Safepharm Laboratories Ltd, 2000p). Six replicate test flasks were prepared for the test substance and three controls. No abnormalities were detected in any of the replicate test samples. Neither biomass or growth rate of *Scenedesmus subspicatus* was adversely affected by the test substance, giving a 96 h EC_{50} of > 1000 mg/L and NOEC of > 1000 mg/L. Analysis of the WAF after 96 h showed a measured concentration of 0.915 mg/L.

The ecotoxicity data indicates the notified chemical is not toxic to algae up to the limit of its water solubility, but appears to be moderately to highly toxic to fish and highly toxic to daphnia, based on measured concentrations.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The environmental hazard from the notified chemical is considered to be low provided that it is used as indicated, and that disposal of used oil takes place via the routes indicated above. As a component of automotive lubricants, the notified chemical has the potential to be released to the environment during lubricant change, but losses during lubricant formulation and transfer to engine crankcases would be small. It is expected that around 86% of the notified chemical would be destroyed through incineration and/or oil recycling activities. About 14% of the material will be used by automobile enthusiasts, and it is expected that much of this, up to 50% (ie 7% of the total import volume), will be released through disposal into landfill, stormwater drains, and other routes. If deposited into landfill the material will be immobilised through adsorption onto soil particles. The material is not readily biodegradable, but in a landfill is expected to slowly degrade through microbiological and abiotic processes. Incineration would produce water vapour and oxides of carbon.

Of the 14% of waste oil produced by DIY enthusiasts, approximately 5% will be disposed of to waterways via the stormwater system. This equates to < 1% of the total import volume of the notified substance or up to 1 tonne that could be expected to enter the aquatic environment. Due to its high Pow and high hydrocarbon content the notified chemical would be expected to associate with suspended organic material which would settle out into the sediments and eventually biodegrade. The notified chemical is not toxic to algae up to the limit of its water solubility, but appears to be moderately to highly toxic to fish and highly toxic to daphnia, based on measured concentrations.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Hazard Assessment

The notified chemical was of low acute oral toxicity in rats (500 mg/kg < LD_{50} < 2000 mg/kg) and was of low acute dermal toxicity in rats (LD_{50} > 2000 mg/kg). It was a slight to moderate skin irritant and a slight eye irritant in rabbits. It was not mutagenic in bacteria and was not clastogenic in CHL cells (chromosome aberration assay) or mouse bone marrow cells (micronucleus assay). In a 4-week oral repeated dose study organ toxicity was ascribed to adaptive effects in the liver with associated thyroid follicular hypertrophy. At doses above 50 mg/kg/day, haematology effects were observed. The NOAEL was considered to be 50 mg/kg/day.

The notified chemical is determined to be a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999a) with respect to acute oral toxicity and risk phrase R22: Harmful if swallowed, is assigned.

Although the notifier was unable to provide formulation details for the lubricant additive package to be imported, a MSDS for a potential product was supplied. This product was classified as an eye irritant according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999a) and assigned the risk phrase R36: Irritating to eyes. Other potential health effects were destruction of the stomach lining, enlargement of the thyroid on repeated ingestion and dermatitis from prolonged or repeated dermal contact. The product also contained diphenylamine at a concentration of less than 1%. According to the NOHSC *List of Designated Hazardous Substances* (National Occupational Health and Safety Commission, 1999b) diphenylamine is not hazardous at this concentration.

Occupational Health and Safety

The potential imported product containing the notified chemical is an eye irritant from a component(s) other than the notified chemical.

The risk of eye irritation in transport or storage workers is considered to be low given that exposure may only occur in the event of accidental spillage.

The risk of eye irritation in workers involved in formulating the final products is limited to exposure to residues in piping and on drum bungs and couplings as the additive package is pumped to a blending vessel or first to a trough. There may also be a risk of eye or skin irritation should exposure occur during clean up of spills. Following blending, package filling is accomplished in a closed system. The system does not require cleanup after each batch. The risk of eye irritation to workers involved in these operations or to maintenance workers should be negligible given that the concentration of the notified chemical in the blend is 1% or less. The risk of acute oral toxicity and systemic toxicity is also judged to be low because the chemical is not handled at hazardous concentrations. Given the frequency of handling by workers, the engineering controls and use of safety glasses, long sleeved shirts, apron and nitrile or neoprene gloves and the low concentration of chemical in the final products, the health risk for formulators and packers would be low. The MSDS for the

notified chemical and the imported product recommend using nitrile or neoprene gloves.

End use of the formulated products, namely, addition or changing of engine oils may result in frequent exposure. However, the risk of adverse health effects including those resulting from secondary ingestion in end use workers is considered to be low given the low levels of the notified chemical in the products.

Public Health

Public exposure to the notified chemical during transport and storage of the imported lubricant additive package and during lubricant blending is anticipated to be low as is the likelihood of adverse health effects. There is a greater opportunity for exposure to members of the public changing the oil in vehicles at home. However, as the oil contains the notified chemical at a concentration of < 1%, adverse health effects are unlikely. The main hazard of the notified chemical is that it is harmful by ingestion and ingestion is possible by children in the domestic environment where oil changes are being conducted. If a 10 kg child ingests 5 mL of a 1% solution of the notified chemical, the dose received (5 mg/kg) is well below that where acute toxic effects occur in rats (LD50 > 500 mg/kg) and the NOAEL for subchronic effects.

13. RECOMMENDATIONS

Hazard classification

The NOHSC Chemicals Standards Sub-committee should consider the following health hazard classification for the notified chemical:

R22: Harmful if swallowed
S20: When using, do not eat or drink

Control measures - OHS

The following safe work practices should be implemented to minimise occupational exposure during handling of the notified chemical:

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

- Personal protective equipment (PPE) should be used on all occasions where exposure to additive packages containing the notified chemical occurs. The notifier recommends nitrile, neoprene gloves. Chemical impervious clothing is also necessary to prevent skin contact. Consideration should be given to the ambient environment, physical requirements and other substances present when selecting protective clothing and gloves. Workers should be trained in the proper fit, correct use and maintenance of their protective gear. PPE guidance in the selection, personal fit and maintenance 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 containing the notified chemical are hazardous to health in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999a), workplace practices and control procedures consistent with State and Territory hazardous substances regulations must be in operation.

14. MATERIAL SAFETY DATA SHEET

The MSDS for 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).

The MSDS were provided by the applicant as part of the notification statement. They are reproduced here as a matter of public record. The accuracy of this information remains the responsibility of the applicant.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the Act, the director must be informed if any of the circumstances stipulated under subsection 64(2) of the Act arise, and secondary notification of the notified chemical may be required. No other specific conditions are prescribed.

16. REFERENCES

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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.
Diffuse beefy red	3 severe	Swelling with lids half-closed	3 mod.	Discharge with moistening of lids and hairs and considerable area around eye	3 severe
		Swelling with lids half-closed to completely closed	4 severe		

IRIS

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

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