File No: NA/722

September 1999

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

CYASORB®UV – 3638

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

CYASORB®UV – 3638

1. APPLICANT

Cytec Australia Holdings Pty Ltd of 7-11 Railway Street BAULKHAM HILLS NSW and Eastman Chemical Company Ltd of 15 Talavera Road NORTH RYDE NSW have jointly submitted a standard notification statement in support of their application for an assessment certificate for CYASORB®UV – 3638.

2. IDENTITY OF THE CHEMICAL

Chemical Name: 4H-3, 1-benzoxazin-4-one, 2,2'-(1,4-phenylene)bis-

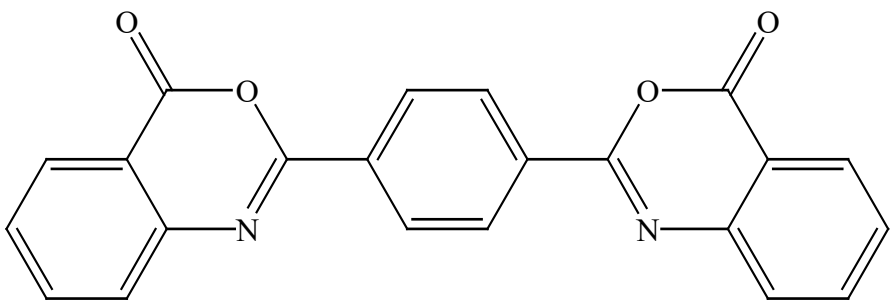
Other Names: 4H-3,1-benzoxazin-4-one, 2,2'- (1,4-phenylenebis-
2,2'-(1,4-phenylene)bis(4H-3,1-benzoxazin-4-one)
2,2'-(p-phenylene)di-3,1-benzoxazin-4-one
2,2'-p-phenylenebis-4H-3,1-benzoxazin-4-one

Chemical Abstracts Service (CAS) Registry No.: 18600-59-4

Marketing Name: CYASORB®UV – 3638
CYASORB®UV – 3638 Light Stabiliser

Molecular Formula: $C_{22}H_{12}N_2O_4$

Structural Formula:



Molecular Weight: 368

Method of Detection and Determination:	Nuclear Magnetic Resonance (^{1}H NMR), Ultraviolet/Visible (UV/Vis) Absorption and Fourier Transform Infrared (FTIR) spectrophotometer
Spectral Data:	an IR spectrum with major absorbance peaks at 1 772,1 619, 1 590, 1 472, 1 255, 1 226, 1 067, 1 002, 767 and 684 cm^{-1}

Comments on Chemical Identity

Reports with ^{1}H NMR, UV/Visible Absorption and IR (Infrared) spectrometric data were submitted for the identification of the notified substance.

HPLC analysis determined the composition of the notified substance, including isomers and by-products.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	off white or pale yellow powder; formed into clear to hazy white pellets for distribution
Melting Point:	315°C
Specific Gravity:	1.4350 at 20°C
Vapour Pressure:	1.5 X 10^{-9} kPa at 25°C
Water Solubility:	<0.112 mg/L at 20°C
Partition Co-efficient (n-octanol/water):	log P_{ow} 4.7 at 22°C
Hydrolysis as a Function of pH:	not determined
Adsorption/Desorption:	K_{oc} >8 590
Dissociation Constant:	not determined
Particle Size:	≤2.003µm = 1.48% ≤10.04µm = 67.43% ≥201.9µm = 11.62% 2.003 to 201.7µm = 86.9% the calculated mass median aerodynamic diameter (MMDA) is 8.03µm and the calculated percentage of

	particles with aerodynamic diameter of <10μm is 63%
Flammability Limits:	not flammable
Autoignition Temperature:	does not self-ignite
Explosive Properties:	not explosive
Reactivity/Stability:	stable; does not possess oxidising properties

Comments on Physico-Chemical Properties

The above tests were conducted according to the EEC Methods for the Determination of Physico-Chemical properties (European Economic Community, 1992) and the OECD Guidelines for Testing of Chemicals (Organisation for Economic Co-operation and Development, 1992). The tests were performed on the CYASORB®UV – 3638 Light Stabiliser, which contains >97% CYASORB®UV – 3638.

The maximum water solubility of CYASORB®UV – 3638 was determined to be < 0.112 mg/L (detection limit) at 20°C using the column elution method (OECD TG 105).

Studies on the hydrolytic stability of the notified chemical were not supplied. However, it is noted that the notified chemical does not contain hydrolysable groups and has very low solubility in water. Therefore, hydrolysis is unlikely under environmental conditions between pH 4 and pH 9.

The partition coefficient log P_{OW} of CYASORB®UV – 3638 between n-octanol and water was estimated to be 4.7 at 22°C by the HPLC method (OECD TG 117).

Three methods were used to calculate the soil adsorption coefficient (K_{OC}) of the notified chemical based on the experimentally determined partition coefficient (P_{OW}). The calculated soil adsorption coefficients (K_{OC}s) were all > 8 590, indicating that the notified chemical will adsorb tightly to organic matter in soil.

The notified chemical contains aromatic nitrogen atoms which are expected to dissociate and associate at various pH. Therefore, the K_{OC} may vary with pH. However, given the magnitude of the calculated K_{OC}, this variation will have little effect on the behaviour of the chemical in the environment where it is expected to be tightly bound to soils and sediment.

Dissociation tests were not conducted due to the low solubility of the notified chemical. The aromatic nitrogens are weakly basic and may increase the solubility at low pH.

4. PURITY OF THE CHEMICAL

Degree of Purity: >97%

Toxic or Hazardous Impurities none known

Non-Toxic or Non-Hazardous Impurities:

Chemical Name	*CAS No.*	*Weight %*
benzoic acid, 2,2'-[1,4-phenylenebis-(carbonylimino)]bis-	3980-13-0	0.1 to 1.0
benzoic acid, 4-(4-oxo-4H-3, 1-benzoxazine-2-yl)	not assigned	0.1 to 0.5
benzoic acid, 4-[[(2-carboxyphenyl)-amino]carbonyl]	not assigned	0.0 to 0.1

Additives/Adjuvants: none known

5. USE, VOLUME AND FORMULATION

The notified chemical, CYASORB®UV – 3638, will not be manufactured in Australia. It will be imported as solid pellets in 20kg or 136kg fibre drums, or in 545kg boxes with polyethylene liners. The notified chemical will be imported initially as a component of CYASORB®UV – 3638 Light Stabiliser at >97%. In future, the notified chemical may be imported as waxy, solid chemical.

The notified chemical will be used as ultraviolet (UV) light absorber and stabiliser of polymeric plastic products. The end use products will contain approximately 1.0 to 3.0% of the notified chemical.

The annual import volume of the notified chemical will be between 500 to 1 000kg for the next 3 years and is expected to exceed 1 000kg in the following 2 years.

6. OCCUPATIONAL EXPOSURE

The notified chemical, CYASORB®UV – 3638, will be imported as a component of the product CYASORB®UV – 3638 Light Stabiliser at >97%. The product comes in a pellet form in fibre drums, or boxes with polyethylene liners. The product will be compounded with other ingredients in an extrusion process to form plastic pellets containing up to 30% of the notified chemical. The plastic pellets will be sold to customers for the production of plastic products. The plastic products would contain approximately 1 to 3 % by weight of the notified chemical.

During importation and reformulation of the pellets containing the notified chemical, the number and categories of workers with potential exposure to the notified are as follows:

waterside workers (5-10 personnel), transport and warehouse (5-10 personnel), plant operators (80-200 personnel) and laboratory technicians (4-10 personnel). Waterside, transport and warehouse workers would not be exposed to the notified chemical under normal circumstances, as they will be handling only the sealed packages.

Formulation of masterbatch pellet

During reformulation, the pellets containing the notified chemical will be compounded with other raw materials to form compounded plastic pellets known as masterbatch. The plant operator manually weighs out the pellets using an aluminum scoop and transfers the requisite amount into plastic bags. The plastic pellets and other ingredients are transferred into a mixer. The mixer is sealed during mixing. After mixing, the extruder operator releases the mixture from the sealed dispenser into the extruder. Alternatively, the mixer may open directly into the extruder below through a sealed tube. In the extruder, the raw materials are melted and mixed. The melted mixture is extruded through die holes in long spaghetti-like strings, passes through a cooling water bath into a pelletiser and classifier, which cuts the strings into pellets, (approximately 5 mm width), graded and conveyed to a hopper for storage prior to bagging.

A quality control technician scoops a portion of the masterbatch into a sample container for testing. The quality of the pellets is tested against a battery of quality control tests using standard laboratory procedures. Following quality control testing, a packaging operator will bag the masterbatch into a 25 kg capacity woven laminated plastic bags, ready for distribution to customers.

All of the workers involved in the production of masterbatch will wear personal protective equipment including dust masks, gloves and overalls. Workers involved in weighing will also wear safety glasses. Dust extraction is employed at the weighing area to minimise inhalation exposure to the notified chemical. The extruder loading area is also fitted with local exhaust ventilation. The laboratory technician will wear protective clothing such as laboratory coat, safety glasses and gloves.

Formulation of plastic products

At the customer site, the masterbatch will be re-extruded using similar extrusion processes described above. The masterbatch will be mixed with other plastics before being mechanically lifted or conveyed to a hopper, or released directly into the melt processing equipment. The mixture will be either injection molded into articles or extruded into sheeting, which can be formed and trimmed as required.

Since the notified chemical is encapsulated in the compounded plastic pellets, worker exposure to the notified chemical during incorporation with plastic products will be unlikely.

7. PUBLIC EXPOSURE

The exposure of the general public to the notified chemical during transport, storage, processing and use is expected to be low. Although the public will make dermal contact with plastic products containing the notified chemical, exposure is expected to be negligible. In addition, the notified chemical is encapsulated and is not expected to leach from the plastic products.

8. ENVIRONMENTAL EXPOSURE

Release

The notifier estimates that up to 5% of the imported material will be wasted due to residues left in import containers (approximately 2%) and spills at the production stage (approximately 3%). This equates to approximately 50 kg of CYASORB®UV – 3638 being lost per year. Spilled materials, being solid and mainly in pellet form, will typically be collected with a broom and bagged. Since the imported product will be used mostly in thermoplastic polymers, the polymer can be remelted and reprocessed. Otherwise, the material will be bagged and disposed of to landfill as normal industrial waste *via* a waste contractor.

For economic and environmental reasons some scrap plastic will be reprocessed and reused in commercial applications. The notifier estimates that <1% of total plastic waste from commercial processing would be released to the environment after recycling. Hence, up to 10 kg of CYASORB®UV – 3638 per year maybe disposed of to landfill as scrap plastic. However, eventually all of the notified chemical will end up in landfill following disposal of the end use plastic products.

Fate

The notified chemical is intended for use as a UV stabiliser in plastics. As such, most of the chemical will share the fate of the plastic articles into which it is incorporated. These will be disposed of to landfill or incineration. Incineration would destroy the chemical and create typical decomposition products of water and oxides of carbon and nitrogen.

A small amount (approximately 20 kg per year) of the notified chemical will be disposed of to landfill as waste from empty containers. The low water solubility of the chemical suggests it is unlikely to leach from landfill. Additionally, once compounded within the polymer matrix, the chemical would not be mobile.

The biodegradability of the notified substance was investigated in a Ready Biodegradability Closed Bottle Test OECD 301D with bacteria-activated sludge from a domestic wastewater treatment plant. CYASORB®UV – 3638 attained an 18% biodegradation after 28 days. The threshold of 60% biodegradation for this test was not achieved within 10 days of achieving 10% biodegradation. Thus, the notified substance was found to be only slightly biodegradable.

A study of bioaccumulation potential for CYASORB®UV – 3638 was not conducted. The notifier states that since the notified chemical is not readily soluble in water, has a log P_{ow} of

4.7 and is not readily biodegradable, it has the potential to accumulate in the environment. Accordingly, care should be taken to avoid release of the notified chemical into the environment. The notifier also states that because the notified chemical will become encapsulated within the polymer matrix, leaching or extraction would be low. Therefore, under normal use and handling of the notified substance there should not be a significant release into the environment.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Summary of the acute toxicity of CYASORB®UV – 3638

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} >5 000 mg/kg	(Blaszcak, 1987b)
acute dermal toxicity	rat	LD_{50} >2 000 mg/kg	(Blaszcak, 1987a)
skin irritation	rabbit	non-irritant	(Parcell, 1995)
eye irritation	rabbit	non-irritant	(Blaszcak, 1987c)
skin sensitisation	guinea pig	weakly sensitising	(Allan, 1995a)

9.1.1 Oral Toxicity (Blaszcak, 1987b)

Species/strain:	rat/Sprague-Dawley
Number/sex of animals:	5/sex
Observation period:	14 days
Dose:	5 000 mg/kg
Method of administration:	10 mL of 50% (w/v) test material in 1% methocel administered orally, via intubation
Test method:	OECD TG 401
Clinical observations:	wet rales observed in females within first 4 hours of dosing; 1 female had a soft stool at 2 hours of dosing; decreased food consumption after dosing in 5 animals which persisted through day 2 in 3 animals; 1 male had a swollen nose on days 3 and 4
Mortality:	nil

Morphological findings:	swollen uterus observed in 1 female after termination
LD_{50}:	> 5 000 mg/kg
Result:	the notified chemical was of very low acute oral toxicity in rats

9.1.2 Dermal Toxicity (Blaszcak, 1987a)

Species/strain:	rabbit/New Zealand White
Number/sex of animals:	6 males and 4 females
Observation period:	14 days
Method of administration:	2 000 mg/kg test substance moistened with 15mL of physiological saline administered by topical application to abraded or intact skin, and held under semi-occlusive dressing; after 24 hours, the treated area was wiped free of excess test material
Clinical observations:	no signs of systemic toxicity noted; 4 males and 3 females exhibited decreased food consumption on the day after dosing, which persisted through day 5 in 3 males and 1 female; slightly decreased body weights noted in 2 animals on day 7, most animals gained weight between day 7 and day 14; animals were scored for skin irritation, as below.

Draize scores (Draize, 1959):

a) Intact skin

Time after treatment (hours)	*Animal #*				
	1M	*2M*	*3M*	*4F*	*5F*
Erythema					
24.5	[a]1	0	1	0	1
72	2	1	1	2	0
7 days	0	0	0	0	0
Oedema					
24.5	0	0	0	0	0
72	0	0	0	1	0
7 days	0	0	0	0	0

[a] see Attachment 1 for Draize scales; M = Male; F = Female

b) Abraded skin

Time after treatment (hours)	*Animal #*				
	1M	*2M*	*3M*	*4F*	*5F*
Erythema					
24.5	[a]1	1	1	1	0
72	0	0	2	0	0
7 days	0	0	0	0	0
Oedema					
24.5	0	0	0	0	0
72	0	0	0	0	0
7 days	-	-	0	-	-

[a] see Attachment 1 for Draize scales; M = Male; F = Female
- scores not noted

Dermal Response:

Intact skin
The severity of the dermal response increased with time with no to slight erythema at 24.5 hours developing into slight to well defined erythema at 72 hours. Oedema was observed in one animal at 72 hours. By day 7 all reactions had resolved.

Abraded skin
Slight erythema at 24.5 hours which had cleared at 72 hours apart from well defined erythema in one animal. By day 7

	all reactions had resolved.
Mortality:	one male died on day 4 due to technical error
Test method:	OECD TG 402
Morphological findings:	postmortem examination of the animal that died during the study revealed clear fluid in the thoracic and abdominal cavities; one animal exhibited green fluid and/or gas in the stomach and intestines at termination
LD_{50}:	> 2 000 mg/kg
Result:	the notified chemical was of low dermal toxicity in rats

9.1.3 Inhalation Toxicity

Claims were made and accepted for Variation of Schedule Requirements for this toxicological endpoint. CYASORB®UV – 3638 will be imported as part of a concentrate within solid plastic pellets or in a waxy pellet form. Therefore, inhalation of the notified chemical is not expected to occur.

9.1.4 Skin Irritation (Parcell, 1995)

Species/strain:	rabbit/New Zealand White
Number/sex of animals:	3 males
Observation period:	4 days
Method of administration:	0.5 g of the test substance moistened with 0.5 mL distilled water was applied to shaved intact skin and held under semi-occlusive dressing; after 4 hours the treatment site was washed with warm water; test sites were examined for evidence of irritation and graded at approximately 1, 24, 48 and 72 hours after treatment
Test method:	OECD TG 404; Annex 5 92/69/EEC
Comment:	no dermal reactions observed in any test animal (all individual scores were zero for oedema and erythema)

Result:	the notified chemical was not irritating to the skin of rabbits

9.1.5 Eye Irritation (Blaszcak, 1987c)

Species/strain:	rabbit/New Zealand White
Number/sex of animals:	non irrigated eyes: 4 males and 2 females; irrigated eyes: 3 females
Observation period:	3 days
Method of administration:	31.1 mg (equivalent to 0.1mL) of test material as supplied instilled into the conjunctival sac of the right eye of each test animal; eyelids were held together for one second; the contralateral eye served as the control; the treated and control eyes of 3 animals were rinsed with lukewarm water 30 seconds after instillation; treated and control eyes for both irrigated and non irrigated eyes were examined and scored for ocular reactions at 24, 48 and 72 hours after instillation
Test method:	OECD TG 405

Draize scores (Draize, 1959):

a) non irrigated eyes

	Time after instillation								
Animal	***24 hours***			***48 hours***			***72 hours***		
Cornea [1]	***o***			***o***			***o***		
1	0			0			0		
2	0f			0f			0		
3F	0f			0f			0		
4	0f			0f			0b		
5F	0f			0ef			0		
6	0f			0f			0		
Iris									
	all individual scores were zero								
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	0	0	0	0	0	0	0	0	0
2	1	0	0	1	0	0	0	0	0
3F	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0
5F	0	0	0	0	0	0	0	0	0
6	1	0	0	0	0	0	0	0	0

[1] see Attachment 1 for Draize scales
o = opacity r = redness c = chemosis d = discharge
b = control eye exhibited iridial changes
e = control eye had a redness score of 1
f = ulceration – zero score confirmed with fluorescein
F = female

a) irrigated eyes

	Time after instillation		
Animal	***24 hours***	***48 hours***	***72 hours***
Cornea [1]	***o***	***o***	***o***
1F	0f	0f	0
2F	0f	0f	0
3F	0f	0f	0
Iris			
	all individual scores were zero		

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

[1] see Attachment 1 for Draize scales
o = opacity r = redness c = chemosis d = discharge
f = ulceration – zero score confirmed with fluorescein
F = female

Comment:

non irrigated eyes slight conjunctival redness was resolved by 72 hours; lack of ulceration of the cornea confirmed with fluorescein at 24 and 48 hour observation

irrigated eyes slight conjunctival redness in one eye was resolved by 72 hours; lack of ulceration of the cornea confirmed with fluorescein at 24 and 48 hour observation

Result: the notified chemical was not irritating to the eyes of rabbits

9.1.6 Skin Sensitisation (Allan, 1995a)

Species/strain: guinea pig/Dunkin Hartley

Number of animals: Males, 20 test, 10 control

Induction procedure:

test group:

day 1	*Intradermal induction* 3 pairs of intradermal injection (0.1mL) into the scapular region of 10 animals: a) Freund's Complete Adjuvant (FCA) and water for irrigation (50:50) b) 5% (w/v) test substance in Alembicol D c) 5% (w/v) in a 50:50 mix of FCA and Alembicol D
day 6	*Topical induction* 0.5mL of 10% (w/w) sodium lauryl sulphate in petrolatum was gently rubbed on the previously injected scapular region of 10 animals
day 7	filter paper containing 0.4mL of the test substance (60% w/v in Alembicol D) was applied to the test site and held in place with occlusive dressing for 48 hours
control group:	control animals were treated identically to test animals but omitting the test substance from the intradermal injection and topical application

Challenge procedure:

day 21 (first challenge)	0.2 mL of 30 and 60% (w/v) test substance in Alembicol D was applied to a site on the posterior and anterior left flank of each animal, respectively; the filter paper containing the test substance was held in place by occlusive dressing for 24 hours; test sites were examined at 24, 48 and 72 hours after test substance application
day 28 (second challenge)	challenge procedure as above

Test method: OECD TG 406; Annex 5 92/69/EEC; Magnusson and Kligman-Guinea Pig Maximisation Test

First challenge:

	*Test animals***			*Control animals***		
Challenge concentration	***24 hours****	***48 hours****	***72 hours****	***24 hours****	***48 hours****	***72 hours****
30%	0/10	5/10	5/10	0/5	0/5	0/5
60%	0/10	1/10	1/10	0/5	0/5	0/5

* time after patch removal
** animals exhibiting at least Grade 1 (Slight erythema) dermal response were counted.

1st Challenge outcome: Given the low dermal response (slight erythema), a 2nd challenge was conducted, using the same concentrations.

Second challenge:

	*Test animals***			*Control animals***		
Challenge concentration	***24 hours***	***48 hours****	***72 hours****	***24 hours****	***48 hours****	***72 hours****
30%	3/10	3/10	3/10	0/5	1/5	1/5
60%	2/10	2/10	1/10	0/5	0/5	0/5

* time after patch removal
** animals exhibiting at least Grade 1 (Slight erythema) or more dermal response were counted

Challenge outcome: At the initial study, animals showing positive responses were not consistent between the 1st and 2nd challenge. Only 3/10 animals showed positive responses at 1st and 2nd challenge. Inconclusive response where 1st challenge showed positive response but negative at the 2nd challenge or vice versa were observed in 6/10 animals. The remaining animal had no dermal response at either 1st or 2nd challenge.

Repeat study

The results of the above challenge procedures were considered to be inconclusive. The study was repeated using another 10 test and 5 control animals, to bring the total number of test animals and control animals to 20 and 10, respectively in accordance with the OECD test guideline. The repeat study was conducted in an identical manner to that of the initial study, except that the second challenge was omitted.

Challenge concentration	Test animals**			Control animals**		
	24 hours	*48 hours**	*72 hours**	*24 hours**	*48 hours**	*72 hours**
30%	1/10	2/10	1/10	0/5	1/5	1/5
60%	0/10	0/10	0/10	0/5	0/5	0/5

* time after patch removal
** animals exhibiting at least Grade 1 (Slight erythema) or more dermal response were counted

Repeat Study - challenge outcome: In this repeat study, 9 test animals showed no evidence of skin sensitisation and 1 animal gave an inconclusive response.

Comment: From the combined results of the first study and repeat study: three animals were positive, seven were inconclusive and the remaining 10 were negative for sensitisation

Result: Based on the positive responses in 3 animals, the notified chemical is considered to be a weak sensitiser to guinea pig skin

9.2.1 28 Day Repeated Dose Toxicity (Allan, 1995b)

Species/strain: rat/Sprague Dawley

Number/sex of animals: 5/sex/dose group

Method of administration: oral (gavage); vehicle was 1% methylcellulose (MC)

Dose/Study design: 10 mL of test substance administered daily for 28 consecutive days

15 mg/kg/day (low dose);
150 mg/kg/day (mid dose);
1 000 mg/kg/day (high dose).

10 mL of 1% MC – vehicle control

There were no recovery groups.

Test method: OECD TG 407

Clinical observations:
There were no deaths during the study. No clinical signs were noted in any of the animals throughout the study. Body weight gain and, food and water consumption was similar to control animals.

Clinical chemistry/Haematology:

Significant changes observed in high dose animals not considered to be treatment-related included: increased neutrophil counts; decreased mean corpuscular haemoglobin concentration (MCHC); decreased thrombotest times; decreased albumin/globulin ratio; and increased creatinine levels

Organ Weights:
Significantly increased liver weights were observed in animals of the mid and high dose groups and considered to be due to congestion (see Histopathology below). In the absence of pathological change, this effect was not considered to be of toxicological importance. There were no significant differences noted in the weights of testes, epididymides, prostate, seminal vesicles and ovaries of treated groups compared with control groups.

Histopathology:

A dose responsive incidence of vacuolation of sertoli cells of some tubules in the testes was observed. However, the incidence did not reach statistical significance using Fisher's Exact test. Atrophy of the testes was also seen in one mid dose male. The vacuolation seen represents a degenerative change in sertoli cells. The study authors reported no change in spermatid morphology. No comment was provided on spermatid concentration.

Further investigations of longer duration of treatment (at least 40 days) and higher doses are required to adequately assess the biological significance of changes in spermatogenesis. To investigate the reversibility or persistence of the vacuolation, a treatment free period is also required.

Non-treatment related pathological findings observed in animals at high dose included: myocarditis; congestion and focal necrosis of the liver; tubular basophilia and dystrophic mineralisation, interstitial inflammatory cell infiltration of the kidney; epithelial hyperplasia and keratin cysts of the stomach; and a distended lumen of the caecum.

Result:
The lesion of the Sertoli cells at all doses in males precludes the establishment of a NOAEL in this study. The Lowest Observed Adverse Effect Level (LOAEL) for males in this study is 15 mg/kg/day.

9.2.2 One Generation Reproductive Study (Turck, 1998)

Species/strain: rat/Sprague Dawley

Number/sex of animals: 30 animals/sex/group

Method of administration: oral (gavage)

Dose/Study design:

1st parental generation (P1):

The test substance was administered daily (dose volume of 5mL/kg/day) to male and female animals for 70 and 14 days before mating, respectively and continued until scheduled euthanasia (approximately day 21 of lactation):

0 mg/kg/day*	(vehicle control 1% methylcellulose);
1 mg/kg/day	(males only, not mated to females)
10 mg/kg/day	(low dose);
150 mg/kg/day	(mid dose);
1 000 mg/kg/day*	(high dose).

*Tissues from these dose groups were examined microscopically.

An additional 10 males treated at 1 000 mg/kg/day served as a satellite group and were euthanised following 28 days of exposure. The testes from these animals were examined microscopically.

1st filial offspring (F1):

The F1 offspring were potentially exposed to the test substance *in utero*, and as F1 neonates during lactation but were not dosed.

On day 21 of lactation, 30 male weanlings (offspring of the control and high dose P1) were selected to be retained to 90 days of age for microscopic evaluation.

Test method:

OECD TG 415

<u>P1 Generation</u>

Mortality:

Mortality, including animals euthanised *in extremis* is presented below:

	Dose Level (mg/kg/day)				
	0	1	10	150	1 000
in extremis;	1M/1F	1M			1M
mechanical injury or technical error;					3M
cause of death unknown.			2M	1M	2M

M = male; F = female.

Clinical observations:
No treatment-related toxicity was observed at any dose. During lactation, a subcutaneous mass was observed in the neck of one female and in the thoracic region of another female at high dose. These masses were not evident at necropsy and were considered not to be treatment-related.

Body weights and food consumption:
No treatment-related changes in body weight or food consumption were noted.

Macroscopic observation:
No treatment-related macroscopic findings were noted.

Organ weight values:
No treatment-related changes in the mean absolute or the mean organ/body weight ratio for all treated animals compared with controls. Uterine weight of high dose females in pro-oestrus at the time of necropsy, was statistically decreased from controls. This was not considered treatment-related since there were no changes in uterine weight noted at any other stage of oestrus.

Microscopic observations:
No treatment-related microscopic findings were observed in animals of the high dose group.

Sperm analysis:
Sperm motility and concentration were comparable between control males and all treated males. No comment was provided on morphology.

Reproductive indices:
There was a slight, non-significant reduction in both the mating (77.8%) and fertility (81.5%) indices in males of the 1 000 mg/kg/day group compared with control values. The fertility and mating indices were within the laboratory historical control range (50 to 100% and 76 to 100%, respectively) and the reduction was not considered treatment related. Females fertility indices such as oesterus cycle, gestation index, and the number of females mated or pregnant were comparable with control groups. A slight increase in copulatory interval (3.6 to 4.6 days) was noted in all treated animals compared with control group (2.3 days); however the values were with in the laboratory historical control range (range 2.0 to 6.1 days) and was not considered treatment related.

Litter data:
No treatment-related changes in numbers of stillborn and live born pups per litter, total litter size, or pup survival was noted during the preweaning interval. There was a slight, non-significant increase in stillborn index (1.4 to 2.1%) in treated groups compared with control group (0.8%) due to one litter that had 6 of 19 pups stillborn. This was not considered treatment related or of biological significance. All other parameters including the 4-day viability index, lactation index and sex ratio (males/total pups) were comparable between controls and treated groups.

Satellite Males

Macroscopic observations:
Macroscopic evaluation of all tissues was reported within normal limits for all animals.

Microscopic observations:
Microscopic evaluation of the testis was reported as within normal limits for all animals.

Preweaning and Postweaning (F1)

Clinical observations:
No treatment-related effects on clinical observations, bodyweight or food consumption were noted for both pre- and postweaned pups during the study.

Macroscopic observation
No treatment-related macroscopic observations were observed in male pups.

Organ weight values:
No treatment-related changes in the mean absolute or the mean organ/body weight ratio for male pups compared with controls. The mean absolute right caudal epididymis and the mean right caudal epididymis/body weight ratio in the low and mid dose, respectively, were significantly decreased. The absolute weight was considered to be spurious and the decrease in organ/body weight ratio was secondary to a slight increase in body weight.

Microscopic observations:
No treatment-related microscopic findings were observed in any of the tissues of male offspring of the control and high dose animals.

Sperm analysis:
Sperm motility and concentration were comparable between the male offspring of the control and high dose animals. No comment on morphology was given.

Summary of findings:
The observed mortality was not considered treatment related as it was not dose related. No treatment related effects were observed in either the P1 or F1 generation on body weight, bodyweight gain or food consumption, or gestation and lactation (in P1 dams). Reproductive indices and litter data were comparable between control and treatment groups, or were within the laboratory historical control range. There was no treatment related effects on sperm motility and concentration in either generation. Furthermore, no treatment-related findings were noted during macroscopic or microscopic examination of tissues. Organ weights were comparable between control and treatment groups, for both generations.

Result:
The notified chemical had no effect on fertility, male and female reproductive performance, parturition, or neonatal viability and growth at any dose level. The no observed effect level (NOEL) determined in this study for the parameters investigated is 1 000 mg/kg/day.

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* Reverse Mutation Assay (Kitching, 1995)

Strains:	*Salmonella typhimurium* TA1535, TA1537, TA98 and TA100
Metabolic activation system:	liver microsomal fraction (S9) from rats pretreated with Aroclor 1254 in Arachis oil
Test method:	OECD TG 471 – plate incorporation method
Experimental design:	the test substance and controls were tested in triplicate using two independent experiments with and without metabolic activation as follows: *without S9* 0, 50, 150, 500, 1 500 and 5 000 μg test substance/plate solvent control: dimethyl sulphoxide (DMSO) positive controls: N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) 9-Aminoanthracene (9AA) 2-Nitrofluorene *with S9* 0, 50, 150, 500, 1 500 and 5 000 μg test substance/plate solvent control: DMSO positive controls: 2-Aminoanthracene (2-AA)
Comment:	no toxicity observed at any concentration; no evidence of mutagenic activity was observed with the solvent control in any of the tests; concurrent positive controls demonstrated the sensitivity of the assay and the metabolising activity of the liver preparations; and there was no marked increase in revertant colony numbers in any of the tester strains, at any test substance concentration, in the presence or absence of metabolic activation.
Result:	the notified chemical was not considered to be mutagenic in the bacterial strains tested with or without metabolic activation

9.3.2 Chromosome Aberration Assay in Human Lymphocyte (Akhurst, 1995)

Cells:	peripheral blood lymphocytes from male donors
Metabolic activation	liver microsomal fraction (S9) from rats pretreated with

system: Aroclor 1254 in Arachis oil

Experimental design: Two independent experiments were conducted in duplicate. The experimental design and concentrations tested are tabulated below:

Metabolic Activation	**Experiment**	**Test substance concentration (μg/mL)**	**Controls**
-S9	Experiment 1	18 hour harvest: 12.5, 25*, 50*, 100* and 200	Positive: EMS – 500 μg/mL Negative: DMSO - 10μL/mL
	Experiment 2	18 hour harvest: 12.5, 25*, 50* and 100* 32 hour harvest: 25, 37.5, 50 and 100*	Positive: EMS – 750 μg/mL Negative: DMSO - 10μL/mL
+S9	Experiment 1	18 hour harvest: 12.5, 25*, 50*, 100* and 200	Positive: CP - 10 μg/mL Negative: DMSO - 10μL/mL
	Experiment 2	18 hour harvest: 12.5, 25*, 50* and 100* 32 hour harvest: 25, 50 and 100*	Positive: CP – 10 μg/mL (18 hour harvest); 5 μg/mL (32 hour harvest) Negative: DMSO - 10μL/mL

EMS - ethyl methanesulphonate
CP - cyclophosphamide
DMSO – dimethylsulphoxide
* - cultures selected for metaphase analysis

Test method:	OECD TG 473
Metaphase analyses and Mitotic index:	cultures selected for metaphase analysis are indicated in the above table
Comment:	crystals of the test substance were observed on slides at all concentrations in Experiment 1; no significant increase in the frequency of chromosomal aberrations at any test substance concentration in the presence or absence of metabolic activation; and all positive controls induced significant increases in the frequency of chromosomal aberrations
Result:	the notified chemical was not considered clastogenic to human lymphocytes *in vitro*

9.4 Overall Assessment of Toxicological Data

Toxicity Summary
The notified chemical, CYASORB®UV – 3638, has very low acute oral toxicity (LD_{50} >5 000 mg/kg) and low dermal toxicity (LD_{50} >2 000 mg/kg) in rats. It was not a skin and eye irritant in rabbits. Acute inhalation studies have not been conducted on the notified chemical. However, inhalation of the notified chemical is not expected to occur, as it will be imported within solid plastic pellets or in a waxy pellet form. Results of an adjuvant type skin sensitisation study were inconclusive for sensitisation in an initial study, but negative in a repeat study under identical test conditions. The notified chemical is considered to be weakly sensitising to guinea pig skin

In a 28 day repeat oral dose study, a dose responsive incidence of vacuolation of sertoli cells of some tubules in the testes was observed in treated males, but did not reach statistical significance. Within the limits of the study design it was not possible to assess the biological significance of this finding. Based on this lesion of the Sertoli cell, the Lowest Observed Adverse Effect Level (LOAEL) in this study is 15 mg/kg/day and a No Observed-Adverse Effect Level (NOAEL) is not established.

The effect of the notified chemical upon reproduction and development was investigated in a one generation reproductive study. For the parameters evaluated, the notified chemical revealed no adverse effects on fertility, male and female reproductive performance, parturition, or neonatal viability and growth at any dose level. The effects on Sertoli cells observed in the 28 day study were not evident in either satellite, parental or filial males of the study. In the absence of adverse treatment related effects, the NOEL for this study was 1 000 mg/kg/day, the highest dose level tested.

The notified chemical was not mutagenic in a bacterial mutation assay or clastogenic in human lymphocytes *in vitro*.

Hazard classification
The results of the acute oral and dermal studies, skin and eye irritation studies, and overall incidence of positive reactions for skin sensitisation are below the thresholds for classification as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999). The treatment related effects observed in repeat dose study were not observed in a second study. The notified chemical is not considered mutagenic *in vitro*. Based on the data submitted, the notified chemical would not be classified as a hazardous substance under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999).

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The notifier has supplied the following ecotoxicity studies. The tests were carried out according to OECD Test Methods.

Test	***Species***	***Test concentrations (nominal) mg/L***	***Results (Nominal) mg/L***
Acute Toxicity (Static Test) (OECD TG 203)	Rainbow Trout *(Oncorhynchus mykiss)*	100	96 h LC_{50} > 100
Acute Toxicity - Immobilisation (Static Test) (OECD TG 202 part I)	Water Flea (*Daphnia magna*)	100	48 h EC_{50} > 100
Growth Inhibition - (Static Test) (OECD TG 201)	Green Algae (*Selenastrum capricornutum*)	100	E_rC_{50} > 100 E_bC_{50} > 100 LOEC > 100
Respiration Inhibition (OECD TG 209)	Activated Sludge - Aerobic Waste Water Bacteria	100	3 h IC_{50} > 100

LC_{50} – median lethal concentration
E_rC_{50} – calculated concentration of test substance which results in a 50% reduction of growth rate r relative to control
E_bC_{50} – calculated concentration of test substance which results in a 50% reduction of biomass b relative to control
IC_{50} – median inhibition concentration

Fish (Bell, 1995a)

A group of 10 fish was exposed to a single nominal concentration of 100 mg/L of CYASORB®UV – 3638. No mortalities or other significant adverse effects were observed. The 96 hour LC_{50} value, based on mean measured concentrations in filtered samples, was determined to be >0.25 mg/L. This was a reflection of the low water solubility of the test substance.

Aquatic Invertebrates (Bell, 1995b)

Daphnia magna were exposed for 48 hours to a single water accommodated fraction (WAF) of CYASORB®UV – 3638. CYASORB®UV – 3638 was initially added at a nominal concentration of 100 mg/L. After one hour of stirring, undissolved material was removed by filtration. No mortalities and other significant adverse effects were observed. The 48 hour LC_{50} value, based on mean measured concentrations in filtered samples, was determined to be >0.27 mg/L. This was a reflection of the low water solubility of the test substance.

Algae (Bell, 1995c)

An algal growth inhibition test was carried out using *Selenastrum capricornutum*. One test culture and one control were exposed to a single WAF of CYASORB®UV – 3638, which was repeated 6 times. The E_rC_{50}, E_bC_{50} and the no observed effect level (NOEL) were all calculated to be >0.024 mg/L based on filtered mean measured concentrations. Yet again this was a reflection of the low water solubility of the test substance. All test and control algal cultures were inspected microscopically at 72 hours. No algal cultures showed abnormalities or signs of contamination by foreign algal cells or protozoa.

Microorganisms (Bell, 1995d)

The inhibitory effect of the notified substance on aerobic wastewater bacteria activated sludge from a domestic wastewater treatment plant was investigated in a respiration test. The notified substance showed essentially no toxic effects. The respiration rate was not inhibited when bacteria were exposed to the test nominal concentration of 100 mg/L over the exposure period of 30 minutes, with a final 3 hour IC_{50} >100 mg/L.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The notified chemical will be used as a UV stabiliser for plastics. Once incorporated into these products the notified chemical is expected to remain within the product matrix. Most of the notified chemical will share the fate of the articles into which it is incorporated. These may be initially be recycled but will eventually be disposed of to landfill or by incineration. In landfill, the notified chemical is expected to remain immobile within the plastic polymer matrix.

Waste from empty containers (total 20kg per annum), product manufacturing (approximately 30 kg per annum) and scrap plastic recycling (approximately 10 kg per annum) will be disposed of to landfill, where the polymer is expected to be immobile, due to the low water solubility.

Hence, the overall environmental hazard of the chemical can be rated as low, given the low environmental exposure.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Assessment of Toxicological Hazard
The notified chemical, CYASORB®UV – 3638, will be imported in pellet form as a component of a product used in plastic manufacture. During further processing, the notified chemical is bound within a polymer (and plastic) matrix.

The notifier provided toxicological studies in support of their application for an assessment certificate. The notified chemical exhibited very low acute oral (LD_{50} >500 mg/kg) and low dermal toxicity (LD_{50} >2 000 mg/kg) in rats. Acute inhalation studies have not been conducted on the notified chemical. Claims were made and accepted for variation of the schedule requirements for this toxicological end point. In rabbits, the notified chemical was not a skin and eye irritant.

The notified chemical is considered to be a weakly sensitiser in guinea pigs.

In a 28 day repeat oral dose study, a dose related but not significant incidence of vacuolation of Sertoli cells of some tubules in the testes was observed in treated males. This effect and other treatment related effects were not observed in a one-generation reproductive study. The Lowest Observed Adverse Effect Level (LOAEL) is 15 mg/kg/day based on the effect in Sertoli cells in the 28 day study.

The notified chemical was not mutagenic in a bacterial mutation assay or clastogenic in human lymphocytes *in vitro*.

Based on the toxicological data submitted the notified chemical would not be classified as a hazardous substance under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999).

Occupational Health and Safety
There is potential for dermal, inhalation and eye exposure when handling the notified chemical; however the notified chemical is presented in solid pellet form that is designed to be anti-dusting. During normal industrial use, inhalation exposure and, skin and eye contamination to the notified chemical is expected to be low.

Waterside, warehouse and transport workers

Under normal working conditions, waterside, warehouse and transport workers will be handling sealed packages of products containing the notified chemical. Therefore, occupational risks for these workers are low.

Plant operators

During reformulation, workers scooping, weighing and adding the pellets containing the notified chemical at 97% to containers in preparation for mixing and extrusion have the highest chance of dermal, inhalation and eye exposure to the notified chemical. Workers involved in other processes, such as extrusion, quality control testing and bagging of plastic pellets, would have lower exposure since after compounding, the notified chemical is present at 30% but it is encapsulated in the masterbatch pellets. The imported product and the masterbatch pellets are described as anti-dusting and should minimise worker exposure to

chemical dust. The notifier states that workers involved in the production of the masterbatch pellets will wear dust masks, gloves and overalls. This equipment will also be sufficient to protect workers from health effects resulting from exposure to the notified chemical. Workers involved in weighing will also wear safety glasses. Dust extraction employed at the weighing area will control inhalation exposure to the notified chemical. The extruder loading area is also fitted with local exhaust ventilation. The laboratory technician will wear protective clothing such as laboratory coat, safety glasses and gloves when carrying quality control tests.

At the customer site, the masterbatch pellets will be re-extruded to form plastic end use products. The notifier did not provide details on the re-extrusion process. However, since the notified chemical is encapsulated within the masterbatch pellets, separate exposure to the notified chemical cannot occur. Similarly, while worker exposure to the plastic products containing the notified chemical may occur, separate exposure to the notified chemical cannot occur.

Public Health
Public contact to the notified chemical will only occur following accidental exposure from a spill and from touching plastic products containing the notified chemical. However, exposure to the notified chemical is assessed as negligible because of the low concentration of the notified chemical in the plastic products. In addition, the notified chemical will be encapsulated within the plastic products from which the notified chemical is not expected to leach, hence the notified chemical is not expected to be dermally absorbed. The potential for public exposure to the notified chemical during all phases of its life cycle is considered to be low.

13. RECOMMENDATIONS

To minimise occupational exposure to CYASORB®UV – 3638 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) and AS 3765.1 (Standards Australia, 1990);
- Impermeable gloves should conform to AS/NZS 2161.2 (Standards Australia, 1998);
- All occupational footwear should conform to AS/NZS 2210 (Standards Australia/Standards New Zealand, 1994);
- Spillage of the notified chemical should be avoided. Spillages 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 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 the Act, secondary notification of the notified chemical shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise. No other specific conditions are prescribed.

16. REFERENCES

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Attachment 1

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

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

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

CORNEA

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

CONJUNCTIVAE

Redness	*Rating*	*Chemosis*	*Rating*	*Discharge*	*Rating*
Vessels normal	0 none	No swelling	0 none	No discharge	0 none
Vessels definitely injected above normal	1 slight	Any swelling above normal	1 slight	Any amount different from normal	1 slight
More diffuse, deeper crimson red with individual vessels not easily discernible	2 mod.	Obvious swelling with partial eversion of lids	2 mild	Discharge with moistening of lids and adjacent hairs	2 mod.
		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