File No: STD/1029

13 March 2003

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

1,3-dimethyl-4-aminouracil

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

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at:

Library
National Occupational Health and Safety Commission
25 Constitution Avenue
CANBERRA ACT 2600
AUSTRALIA

To arrange an appointment contact the Librarian on TEL + 61 2 6279 1161 or + 61 2 6279 1163.

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

Street Address: 334 - 336 Illawarra Road MARRICKVILLE NSW 2204, AUSTRALIA.
Postal Address: GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL: + 61 2 8577 8800
FAX + 61 2 8577 8888.
Website: www.nicnas.gov.au

Director
Chemicals Notification and Assessment

TABLE OF CONTENTS

FULL PUBLIC REPORT

1,3-dimethyl-4-aminouracil

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
Crompton Specialties
462 Burwood Road
Hawthorn VIC 3123

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:
Spectral data
Purity
Non hazardous impurities
Import volume

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:
Vapour pressure
Adsorption/desorption
Dissociation constant
Flash point
Acute inhalation toxicity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
CEC Permit No 550

NOTIFICATION IN OTHER COUNTRIES
EINECS (EU), USA (2001), Philippines 1996, Japan ENCS

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
1,3-dimethyl-4-aminouracil

OTHER NAME(S)
6-Amino-1,3-dimethyl-2,4 (1H, 3H)-pyrimidinedione
1,3-Dimethyl-2,6-dioxo-4-aminopyrimidine
1,3-dimethyl-6-aminouracil
TKA 40179

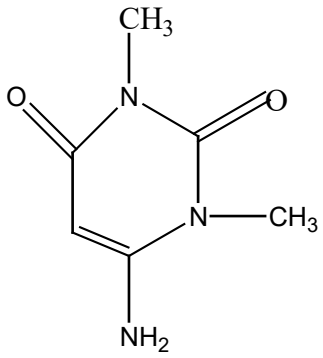
MARKETING NAME(S)
CD 19-0456
OBS (preparation)

CAS NUMBER
6642-31-5

MOLECULAR FORMULA

$C_6H_9N_3O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
155.14

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD UV, NMR and IR spectrum

3. COMPOSITION

DEGREE OF PURITY
>90%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported either neat or as a granular preparation containing between 20 to 80% of the chemical

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	3-10	10-30	30-100	30-100	>100

USE
The notified chemical will be used in the plastics industry as an additive in PVC pipes.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, Transport and Storage

TRANSPORTATION AND PACKAGING
The notified chemical is stored and transported in polyethylene bags (25-500 kg). The preparation containing notified chemical will be packed into multi wall paper bags, 20 kg initially and then into re-usable (PVC or similar heavy duty plastic) bulk bags of 500 kg.

5.2. Operation Description

Neat notified chemical
Where the notified chemical is imported neat, the customer (not specified) will formulate the chemical into the stabiliser system and then into pipes:

Reformulation of the stabiliser product
The notified chemical is weighed and then transferred into the mixer. The notified chemical is mixed with other additives at room temperature and then transferred via a receiver hopper to a pelletiser. Packing off the pellets is done via an automated bagging unit (25-20 bags) or using a support frame placed directly under the hopper for the loading of 500 kg bulk bags. The percentage of notified chemical in the final product is between 10 and 30%. The process is semi continuous and is only disrupted when there is a product change.

Formulated notified chemical
Where the notified chemical is imported formulated, granules (of masterbatch) are available directly for end-use.

PVC Pipe Production (End use)

- At the customer's pipe plant, the masterbatch pellets are dry mixed with PVC resin and other additives using an intensive mixer. This resultant mixture is then extruded to produce PVC pipe.

Off-cuts or out-of-specification pipe is milled into a coarse powder. This powder is blended off into less critical products, such as inner fill or twin-wall pipes.

5.3. Occupational exposure

Exposure Details
The notifier did not submit information on the number of workers and worker exposure at the facilities operated by the customers.

Worker exposure may occur during the following activities:

- During formulation of masterbatch, worker exposure to notified chemical (neat chemical) may occur during charging of mixers, weighing and sampling, if it is undertaken, and from packaging the finished pellets containing notified chemical.
- During use of the finished pellets, worker exposure to the pellets may occur when weighing, transferring and during extrusion of PVC pipe.

Engineering controls such as enclosure and local exhaust ventilation will be used in the masterbatch formulation plant and during PVC pipe production.

Workers will wear chemical protective gloves such as PVC or rubber, chemical resistant protective clothing and eye protection such as dust tight safety goggles. Respiratory protection such as dust mask may be worn.

5.4. Release

RELEASE OF CHEMICAL AT SITE
The notified chemical is not manufactured in Australia so there will be no release from this activity. However, the neat imported notified chemical will be used in the production of pelletised stabiliser formulations. During this stage the potential sources of release are: spills, residues in the empty imported bags, dust generation and process equipment cleaning effluent. Spilt material will be swept up and either be returned to the process (if not contaminated) or placed in a sealable labelled container ready for disposal. Less than 0.2% is likely to be lost due to spills. The formulation process will be performed under vacuum extraction/filtration so that any particulate matter released to the air during operations would be captured and retained on the filters, subsequently all solid material retained on the filters would be disposed of. It is estimated that less than 0.1% of the notifier chemical will be lost due to dust/particulate generation. If the process equipment needs cleaning this will be done using

industrial vacuum cleaners with the collected material being reintroduced into the process or going to waste stockpile for disposal. It is estimated that less than 0.1% of the notifier chemical will be lost due to equipment cleaning. Less than 0.1% will be lost due to residuals in the imported empty bags. The bags will be stockpiled for disposal.

Both the produced stabiliser formulation and the imported preparation will be used in the extrusion of piping. The sources and potential quantities of release during pipe manufacture are the same as for the formulation production, however, an additional source is piping off cuts or out of specification product. Generally this material will be ground and re introduced into the process or used to make a less critical product.

RELEASE OF CHEMICAL FROM USE

Once incorporated into PVC pipe the notified chemical will be immobilised in the polymer matrix and little release is expected. Ultimately, the notified chemical will be disposed of with the piping once it has reached the end of its useful life.

Some release of the chemical is possible as a result of "blooming" from the manufactured articles (PVC pipes) during its life. This process is effectively the slow diffusion of the chemical from the interior of the plastic article to the surface, where, in the case of piping, it may be removed through the movement of water or other liquids (including effluent, rainwater, runoff and seepage) as well as cleaning processes and handling and consequently may enter the environment.

5.5. Disposal

The waste generated during the formulation production and pipe production (as indicated in Section 5.4) will go to landfill or, possibly in a few cases, be incinerated. This represents well less than 100 kg of notified chemical annually.

At the end of their useful life, the pipes containing the notified chemical, are likely to be disposed of to landfill.

5.6. Public exposure

The notified chemical and formulations will not be made available to the public. Once incorporated into masterbatch pellets, the notified chemical will not be bioavailable.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Light yellow coloured powder

Melting Point 299ºC

METHOD	OECD TG 102 Melting Point/Melting Range. EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Thermal analysis was performed by Differential Scanning Calorimeter The preliminary test showed that melting was observed at 304.7ºC. The sample lost about 62% of its mass and the colour of the sample was brownish and carbonised In the first and second main test run, the melting points were determined at 399.4ºC and 298ºC, respectively. After measurement, both samples were coloured brownish yellow and a clear melt.
TEST FACILITY	RCC (2002a)

Density 1.434 kg/m^3 at 20ºC

METHOD	OECD TG 109 Density of Liquids and Solids. EC Directive 92/69/EEC A.3 Relative Density.
Remarks	The study was conducted by means of a gas comparison pycnometer. The determination of the relative density of the test item was performed with 2 independent test item samples each at least measured in triplicate.
TEST FACILITY	RCC (2002b)

Vapour Pressure 1.0 x 10^{-4} kPa at 25°C (or 20°C).

METHOD OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.

Remarks The vapour pressure was calculated from the boiling point using the Modified Watson Correlation. An estimated minimum boiling point value of 400°C was assumed in the calculations.

The result indicates that the material is not considered volatile.

TEST FACILITY RCC (2002c)

Water Solubility 5.5 g/L at 20°C

METHOD In-house method, approximates OECD TG 105 Water Solubility – Flask method.

Remarks Analytical Method: HPLC

A series of Erlenmeyer flasks containing 3 g of test material and 50 mL of deionised water were stirred for 24 hours at 30°C. The temperature was then dropped to 20°C and stirring continued. After 24, 48 and 72 hours the contents of a flask was centrifuged and an aliquot of the supernatant taken for analysis.

The result indicates that the test material is readily soluble in water.

TEST FACILITY Vinyl Additives GmbH (1998)

Hydrolysis as a Function of pH

METHOD OECD TG 111 Hydrolysis as a Function of pH.
EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

PH	*T (°C)*	*% Hydrolysis after 5 days*	*$t_{½}$, 25°C (estimated)*
4	50	<10	> 1 year
7	50	<10	> 1 year
9	50	<10	> 1 year

Remarks The half-life was estimated using the EEC directive method. The test material (notified chemical) can be considered to be hydrolytically stable.

TEST FACILITY RCC (2002d)

Partition Coefficient (n-octanol/water) log Pow at 20°C = -0.4

METHOD OECD TG 107 Partition Coefficient (n-octanol/water), Shake flask Method.
EC Directive 92/69/EEC A.8 Partition Coefficient.

Remarks Analytical Method: HPLC

Three (3) tests in duplicate were undertaken at 20°C with the solvent ratios being 1:1, 2:1 and 1:2.

The mass balance recovery ranged from 99 to 102%.

The resultant log P_{ow} indicates that the test material is hydrophilic and will partition to water generally.

TEST FACILITY RCC (2002e)

Adsorption/Desorption $K_{oc} \geq 38$, $_{log}K_{oc} \geq 1.58$.

METHOD In-house estimation – regression equations from Lyman et al. Handbook of Chemical Property Estimation Methods (1990)

Remarks The estimation was based in the water solubility using regression equations (below) and the molecular weight (156.16 g/mol).

Regression I: $\log K_{oc} = -0.55 \log S + 3.64$ (S in mg/L)
Regression II: $\log K_{oc} = -0.54 \log S + 0.44$ (S in mole fraction)
Regression III: $\log K_{oc} = -0.557 \log S + 4.277$ (S in μmole/L)

The repot indicates that the test material is likely to be slightly mobile in soil and sediments.

TEST FACILITY RCC (2002f)

Dissociation Constant pKa = 7.0, primary amine.

METHOD In-house – Taft and Hammett Correlations
Remarks The molecular structure of the test material was used to estimate the dissociation behaviour and thus its dissociation constant. Its structure indicated that there was one possible site for protonation, ie the primary amino group.
TEST FACILITY RCC (2002g)

Particle Size Range between 250 and 2000 μm with 50% exceeding 500 μm.
(2% was <250 μm)

METHOD EC:Particle Size Distribution/Fibre Length and Diameter Distribution Guidance Document.
Remarks The study was performed using the sieving apparatus. Upon visual inspection, the notified chemical forms various size agglomerates.

Only 2.14 and 1.52%, respectively, passed the 250 μm sieve
TEST FACILITY RCC (2002h)

Flash Point Not applicable to solids

Flammability Limits Not highly flammable-

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).

Remarks The notified chemical could not sustain a burning reaction during the preliminary test. Upon contact with the ignition source, the notified chemical melted slowly and white fume was observed. A yellowish to orange flame sustained burning for about 7 seconds and extinguished spontaneously.
TEST FACILITY RCC (2002i)

Autoignition Temperature The notified chemical is not autoflammable

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks Using a linear increase in temperature of about 0.5ºC/min, the notified chemical showed no exothermic reaction.
TEST FACILITY RCC (2002j)

Explosive Properties The notified chemical is not classified as explosive

METHOD
Remarks The explosive properties were estimated based on the UN Recommendations on the Transport Goods Manual
TEST FACILITY RCC (2002k)

Reactivity

Remarks The notified chemical does not have oxidising properties

There are no incompatibilities with other substances
The notified chemical is considered stable

TEST FACILITY RCC (2002l)

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral*	low toxicity LD_{50} >5000 mg/kg bw
Rat, acute dermal	low toxicity LD_{50}>2000 mg/kg bw
Acute inhalation	Not submitted
Rabbit, skin irritation*	non-irritating
Rabbit, eye irritation*	non-irritating
Guinea pig, skin sensitisation - adjuvant test	no evidence of sensitisation.
Rat, oral repeat dose toxicity - 90 days	NOAEL 104 mg/kg/day
Genotoxicity - bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration	genotoxic without S9 to human lymphocytes
Genotoxicity – in vitro cell mutation	non genotoxic (positive responses only seen at toxic doses)
Genottoxicity- in vivo mouse micronucleus	non genotoxic
DNA Synthesis	retardation of the cell cycle

* Not conducted according to OECD guidelines

7.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical

METHOD Acute Oral Toxicity
Species/Strain Rat/Wistar
Vehicle 0.5% aqueous carboxymethyl cellulose
Remarks - Method Single oral administration by gavage
Animals were observed for 14 days
The animals were observed for signs and symptoms. Necropsy and gross pathological examination was conducted

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
	5 males	5000	None
	5 females	5000	None

LD50 >5000 mg/kg bw
Signs of Toxicity No abnormal signs recorded.
Effects in Organs No abnormalities were detected.
Remarks - Results No bodyweight changes were reported.

CONCLUSION The notified chemical is of low toxicity via the oral route.

TEST FACILITY BASF Aktiengesellschaft (1987a)

7.2. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical

METHOD OECD TG 402 Acute Dermal Toxicity.
92/69/EEC, B.3. Acute Dermal Toxicity
Species/Strain Rat/Wistar
Vehicle Purified water
Type of dressing Semi-occlusive.

Remarks - Method	Observation period: 14 days

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
	5 males and 5 females	2000	None

LD50	>2000 mg/kg bw
Signs of Toxicity	No clinical signs were observed during the observation period
Effects in Organs	No macroscopic findings were observed at necropsy
Remarks - Results	

CONCLUSION The notified chemical is of low toxicity via the dermal route.

TEST FACILITY RCC Ltd (2002m)

7.3. Acute toxicity – inhalation

Not submitted

7.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD Based on OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/White Vienna
Number of Animals	3 (1 male and 2 females)
Vehicle	Distilled water
Observation Period	72 hr
Type of Dressing	Semi-occlusive.
Remarks - Method	Animals were exposed for 4 hr to 50% notified chemical in aqueous formulation. The readings were recorded at 30-60 minutes after removal of the test patches and 24, 48 and 72 hr after the beginning of application

RESULTS

Remarks - Results	The mean scores calculated at 24, 48 and 72 hrs were zero for erythema and oedema.

CONCLUSION The notified chemical is non-irritating to skin.

TEST FACILITY BASF Aktiengesellschaft (1987b)

7.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.

Species/Strain	Rabbit/White Vienna
Number of Animals	2 males and 1 female
Observation Period	72 hrs
Remarks - Method	Readings 1, 24, 48 and 72 hrs.

RESULTS

Remarks - Results	The mean scores calculated at 24, 48 and 72 hrs were zero for cornea, iris and conjunctiva.

CONCLUSION The notified chemical is non-irritating to the eye.

TEST FACILITY BASF Aktienegsellschaft (1987c)

7.6. Skin sensitisation

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 406 Skin Sensitisation –Magnussen and Kligman maximisation study EC Directive 96/54/EC B.6 Skin Sensitization
Species/Strain	Female Guinea pig/Albino
PRELIMINARY STUDY	Maximum Non-irritating Concentration: 10% intradermal: 10%, 20%, 30% topical: 50%, 25%, 15% and 10%
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 5
INDUCTION PHASE	Induction Concentration: intradermal injection 10% notified chemical in water topical application 50% notified chemical in water (occlusive dressing)
Signs of Irritation	
CHALLENGE PHASE	After 2 weeks of induction
1st challenge	topical application: 25 % notified chemical in water (occlusive dressing)
2nd challenge	topical application:
Remarks - Method	Cutaneous reactions were evaluated at 24 and 48 hrs after removal of the dressing

RESULTS

Remarks - Results	No toxic symptoms were evident in the guinea pigs of the treated group. None of the animals showed skin reactions after the challenge treatment at 25% notified chemical in water.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	RCC Ltd (2002n)

7.7. Ninety-day repeat dose oral toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain	Rats/Wistar
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 91 days (males) or 92 days (females); Dose regimen: 5/7 days per week; Post-exposure observation period: Recovery period: 28 days
Vehicle	
Remarks - Method	

RESULTS

Group	*Number and Sex of Animals*	*Dose*		*Mortality*
		mg/kg bw/day	*ppm*	
I (control)	10 males and 10 females	0	0	None

II (low dose)	10 males and 10 females	23 (males), 28 (females)	500	None
III (mid dose)	10 males and 10 females	104 (males), 121 (females)	2000	2
IV (high dose)	10 males and 10 females	646 (males), 753 (females)	10000	None
V (control recovery)	10 males and 10 females	0	0	None
VI (high dose recovery)	10 males and 10 females	646 (males), 753 (females)	10000	None

Mortality and Time to Death

No treatment related mortality occurred during the study period. Two deaths occurred among 2000 ppm treated females due to injury in the urinary bladder and kidneys.

Clinical Observations

At 10000 ppm, hunched posture and piloerection were observed. Decreased body weights were noted throughout treatment. During the recovery period, there were no significant differences in body weight.

No clinical signs of toxicity or behavioural changes was noted in the 500 and 2000 pm dose groups over the treatment or recovery period.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

At 10000 ppm, total protein, globulin and serum levels for glucose and urea were decreased in males and females after 13 weeks. Increases in MCV parameters were seen at 1000 ppm (haematology). However, there were no dose relationship established.

Significant changes were seen in clinical biochemistry parameters (sodium, potassium, chloride, inorganic phosphate, calcium and alkaline phosphatase). However, the changes were mild and a dose-response relationship could not be established. These changes were not considered to be treatment related.

Macroscopic investigations

Incidental findings were noted in both treated and control animals. The reported findings were not considered to be significant.

Effects in Organs

After 13 weeks, autopsy body weights were decreased in males and females receiving 10000 ppm. There was an increase in the relative kidney wt in males and females at 10000 ppm and a decrease in testes wt at 10000 ppm.

Microscopic Examinations

Hepatocyte apoptosis (7/10), karyomegaly (5/10) and hepatocyte mitosis (3/10) were increased in incidence in females treated at 10000. Also, 2 females had minimal basophilic foci of cellular alteration in the liver at 10000 ppm. Only one male treated at 10000 ppm showed a minimal degree of karyomegaly.

Following the recovery period, minimal apoptosis was seen in 4/10 females accompanied by minimal mitosis in 2/4 females of the 10000 ppm dose group.

In the adrenal cortex, vacuolation of the zona glomerulosa was recorded in rats of both sexes (8/10 males and 10/10 females) at 10000 ppm. Following the recovery period, these findings had reversed partially (5/10 males and 6/10 females).

Remarks – Results

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 121 mg/kg bw/day (2000 ppm) in this study, based on effects seen on body weight, haematology, clinical biochemistry, organ weight and pathological investigations at 10000 ppm.

TEST FACILITY	NOTOX B.V. (1998a)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 and 472 Bacterial Reverse Mutation Test.
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2 uvrA
Metabolic Activation System	S9 mix
Concentration Range in Main Test	a) With metabolic activation: 100, 333, 1000. 3330 and 5000 µg/plate b) Without metabolic activation: 100, 333, 1000, 3330 and 5000 µg/plate.
Vehicle	Dimethyl sulphoxide
Remarks - Method	*Dose range finding study:* Doses: 3, 10, 33, 100, 1000, 3330 and 5000 µg/plate with and without S9

RESULTS

Remarks - Results	*Range finding study:* No reduction of the bacterial lawn and no decrease in the number of revertants were observed. Main test: The notified chemical did not precipitate in the top agar. The notified chemical showed a negative response both with and without S9.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	NOTOX B.V. (1997a)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosomal Aberration Test. EEC Directive 67/54 Evaluation of the Ability of TKA 40179 (D 19-456) to induce chromosome aberrations in cultured peripheral human lymphocytes (with independent repeat)
Cell Type/Cell Line	Human lymphocytes
Metabolic Activation System	Aroclor-1254 induced rat liver S9-mix
Vehicle	Dimethyl sulphoxide
Remarks – Method	*Dose range finding study:* Doses tested: 100, 333, 1000, 3330, 5455 µg/mL with and without S9 With S9 mix: 3 hr treatment time with 24 hr fixation time Without S9 mix: 24 hr or 48 hr treatment time with 24 and 48 hr fixation time

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Fixation Time*
Experiment 1			
Absent			
Test 1	100*, 333, 560, 1000*, 1778*, 2140	24 hr	24 hr
	333, 560*, 1000*, 1778* and 2140	48 hr	48 hr
Present			
Test 1	1000*, 3330*, 5000*	3 hr	24 hr
Test 2	5000*	3 hr	48 hr
Experiment 2			
Absent			
Test 1	100*, 333*, 560*, 1000, 1333, 1778 and 2140	24 hr	24 hr
Present			
Test 1	1000*, 3330* and 5000*	3 hr	24 hr

* Doses selected for scoring chromosome aberrations

RESULTS

Dose range finding study:
The highest dose was chosen to be 5000 μg/mL: inhibition of mitotic index was shown is >50%.

Experiment 1:
Without S9 mix:

- Induced increases in the frequency of chromosomal aberrations at all concentrations- dose response demonstrated with the 48 hr treatment time with 48 hr fixation time
- No changes in the frequency of chromosomal aberrations at all concentrations for the 24 hr treatment time with 24 hr fixation time

With S9 mix

- No changes in the frequency of chromosomal aberrations at all concentrations for the 3 hr treatment time with 48 hr fixation time

Experiment 2:

No changes with and without S9.

Remarks - Results

CONCLUSION

The notified chemical was clastogenic to human lymphocytes treated in vitro under the conditions of the test for 48 hrs treatment time and 48 hrs fixation time.

TEST FACILITY

NOTOX B.V. (1997b)

7.10. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 476 In vitro Mammalian Cell Gene Mutation Test.
EEC Directive 87/302/EEC

Cell Type/Cell Line: L5178Y mouse lymphoma cells
Metabolic Activation System: Aroclor-1254 induced rat liver S9-mix
Vehicle: Dimethyl sulphoxide
Remarks – Method: *Dose range finding study:*

- Doses tested: 33, 100, 333, 1000, 3330, 5000 μg/mL with and without S9 mix
- 3 hr exposure

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Expression Time*	*CellPlating*
Absent				
Test 1	333*, 1000*, 3330* and 5000*	24 hr	2 days	3 days
Test 2	333*, 1000*, 1778*, 2344, 3330* and 5000	24 hr	2 days	3 days
Present				
Test 1	333*, 1000*, 3330* and 5000*	3 hr	3 days	3 days
Test 2	333*, 1000*, 3330* and 5000*	3 hr	3 days	3 days

* Not selected for mutant measurement frequency

RESULTS

Dose range finding study:
The highest dose was chosen to be 5000 μg/mL: inhibition of mitotic index was shown is >50%

Experiment 1:
Without S9 mix:

- The cell count of the dose 5000 μg/mL was reduced by 67%. The cloning efficiency of the remaining cells directly after treatment showed a reduction of 95%.
- At 5000 μg/mL, there was an 8-fold significant increase in the mutant frequency at the TK-locus. The actual survival of the cells after treatment was only 1.6% (5% of 32%).

With S9 mix:

- No reduction was observed in the cell count at any dose tested. No reduction in the number of colonies was observed in the cloning efficiency of the remaining cells.
- The notified chemical induced a 3-fold increase in the mutant frequency at the TK locus at 5000 μg/mL.

Experiment 2:

Without S9 mix:

- The cell count of 3330 μg/mL was reduced by 63%. The colony efficiency of the remaining cells directly after treatment showed a reduction of 68%.
- At 1778 and 3330 μg/mL, there was a 3-fold significant increase in the mutant frequency at the TK-locus. The actual survival of the cells after treatment of 1778 and 3330 μg/mL was 9 and 12%, respectively.

With S9 mix:

- No reduction was observed to the cell count. In the cloning efficiency of the remaining cells, no clear reduction in the number of colonies was observed.
- No increase in the mutant frequency at any dose level tested was reported.

Remarks – Results

The notified chemical was reported to induce mutant frequencies only at toxic doses. A dose-response was not established in any of the tests.

CONCLUSION

The notified chemical was not clastogenic to L5178Y mouse lymphoma cells treated in vitro under the conditions of the test.

TEST FACILITY

NOTOX B.V. (1997c)

7.11. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test. EEC Directive 67/548/EEC
Species/Strain	Mice/
Route of Administration	Oral intubation
Vehicle	1% w/v carboxymethylcellulose
Remarks - Method	• Single oral intubation • Bone marrow was sampled at 24 and 48 hrs after dosing Dose range finding study: Two dose groups (3 males and 3 females) received a single dose of 2000 and 1000 mg/kg bw and were observed over 3 days. Protocol deviation: Due to mortality occurring in group III, one animal from group II was allocated to group III

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time Hours*
I	5 males and 5 females	500	24 and 48 hrs
II	5 males and 5 females	1000	24 and 48 hrs
III	5 males and 5 females	2000*	24 and 48 hrs

* MTD: maximum tolerated dose

RESULTS	
Doses Producing Toxicity	No decrease in the ratio of PCE/NCE[1] ratio compared to controls
Genotoxic Effects	No increase in the frequency of MPCE[2] was observed in any of the treated animals
Remarks - Results	Animals treated with 500 mg/kg bw notified chemical showed no abnormalities. Two female mice died in group III
CONCLUSION	The notified chemical was not mutagenic in this in vivo micronucleus test under the conditions of the test.
TEST FACILITY	NOTOX B.V. (1998b)

ADDITIONAL INVESTIGATIONS

7.12. DNA synthesis

TEST SUBSTANCE	Notified chemical
METHOD	Analysis of cell-cycle distribution of Chinese Hamster Cells by Flow Cytometry
Cell Type/Cell Line	Chinese Hamster Ovary
Vehicle	Dimethyl sulphoxide
Remarks - Method	Doses: 100, 333, 560, 1000 and 1778 µg/mL No metabolic activation
RESULTS	
Remarks - Results	At 1778 µg/mL, the proportion of cells in the $G_{1/0}$-phase was increased by

[1] Polychromatic erythrocytes/normochromatic erythrocytes
[2] Miconucleated polychromatic erythrocytes

about 53%. This indicates that these cells were hindered or delayed to enter the S-phase. The proportion of cells in the G_2+M=phase was similar to the control. At lower concentrations, smaller changes in the proportions of the $G_{1/0}$- and S- phase were also noted.

The study reported that a calculation showed that at high concentrations, the delay or partial block in $G_{1/0}$ caused an increase of the mean G_1-phase by a factor of about 1.5.

The number of cells at the end of treatment was clearly reduced indicating that a retardation of the cell cycle will have occurred during treatment.

CONCLUSION The notified chemical caused a concentration-dependent effect on the cell cycle in CHO cells treated in vitro under the conditions of the test.

TEST FACILITY Novartis Crop Protection AG (1998)

7.13. Statement on Mutagenicity

In the chromosome aberration test with 48 hrs of treatment, chromatid and chromosome breaks were observed at cytotoxic concentrations. The notified chemical caused a marked disturbance of the cell cycle, but there was no block in the early S-phase. It is suggested that the results are not consistent with the scenario of an inhibition of pyrimidine nucleotide synthesis by the notified chemical. However, there is evidence that the cell cycle was delayed or blocked at one or more sites.

The report suggested that the chromosome breaks observed at high concentrations are artefacts due to the environment of cell cultures.

The notified chemical did not induce the frequency of micronucleus in bone marrow after treatment.

The statement concluded that the notified chemical showed no mutagenicity in bacteria and cultured mammalian cells in vitro.

TEST FACILITY Ciba Specialty Chemicals Inc. (1998)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE 1,3-Dimethyl-4-aminouracil (CD 19-0456)

METHOD OECD TG 301 A Ready Biodegradability: DOC Die-Away Test.

Inoculum	Aerobic activated sludge from a predominantly domestic wastewater treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	DOC analysis by Shimadzu TOC-500 Analyser
Remarks - Method	Sodium benzoate was used as a reference substance.

The flasks were set-up as follows:

Flask	Amount of Material		Measured DOC
	Test Sub. (mg/L)	Ref. Sub (mg/L)	on day 0 (mg/L)
Test Sub.	63	0	28.4
Test Sub.	63	0	28.5
Ref. Sub.	0	50	27.6
Ref. Sub.	0	50	27.6

Inoculum blank	0	0	0.9
Abiotic control	63	0	28.4
Toxicity control	63	50	57.1

Note: the abiotic control flask was poisoned with 10 mg/L mercury dichloride.

Each flask was loosely covered with aluminium foil and incubated in a dark temperature controlled room at 22-23ºC. The pH in the flasks was 7.4 prior to incubation and 7.3 after.

Samples (10 mL) for DOC analysis were taken on day 0, 3, 7, 10, 14, 21, 27 and 28

RESULTS

Test substance		*Sodium benzoate*	
Day	*% degradation*	*Day*	*% degradation*
0	0	0	0
28	0	7	99

Abiotic control		*Toxicity control*	
Day	*% degradation*	*Day*	*% degradation*
0	0	0	0
28	0	14	50

Remarks - Results

The reference substance (sodium benzoate) reached 99% degradation within 7 days, which supports the validity of the test.

The results of the toxicity control indicate that the test substance is not inhibitory to activated sludge since the degradation was greater than 35%

CONCLUSION

Under these study conditions the test substance was not readily biodegradable, but not inhibitory to activated sludge organisms.

TEST FACILITY

RCC Ltd (2001a)

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE

1,3-Dimethyl-4-aminouracil (CD 19-0456)

METHOD

OECD TG 203 Fish, Acute Toxicity Test – static.

Species	Zebra Fish (*Brachydanio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC analysis with UV/VIS-detection
Remarks – Method	A preliminary test was done to ascertain the concentration of the test material to be used.

The test consisted of 2 glass aquarium with 5 litres of medium, each with 7 fish. The fish were not fed during the study and the temperature, dissolved oxygen and pH maintained throughout the study. The aquariums were slightly aerated but there was no renewal of test medium.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	-	7	0	0	0	0	0
100	-	7	0	0	0	0	0

LC50	>100 mg/L at 96 hours.
NOEC (or LOEC)	≥ 100 mg/L at 96 hours.
Remarks – Results	The test medium was a clear solution throughout the study. No abnormal behaviour or dead fish were observed during the study.

CONCLUSION The LC_{50} result indicates that under the Globally Harmonised System of Classification and Labelling of Chemicals the test substance is not classified as harmful to aquatic life.

TEST FACILITY RCC Ltd (2002o)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE 1,3-Dimethyl-4-aminouracil (CD 19-0456)

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – static test.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - static test.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC analysis with UV/VIS-detection
Remarks - Method	A preliminary test was done to ascertain the concentration of the test material to be used. The study was conducted in duplicate with covered glass beakers containing 50 mL of test medium. Each beaker contained 10 daphnia (i.e. 20 daphnia per concentration), which were not fed during the study. The temperature, dissolved oxygen and pH were measured at the beginning and end of the study.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0 (control)	-	20	0	0
100	-	20	0	0

LC50	>100 mg/L at 48 hours
NOEC (or LOEC)	≥ 100 mg/L at 48 hours
Remarks - Results	The test medium was a clear solution throughout the study. No abnormal behaviour or dead daphnia were observed during the study.

CONCLUSION The LC_{50} result indicates that under the Globally Harmonised System of Classification and Labelling of Chemicals the test substance is not classified as harmful to aquatic life.

TEST FACILITY RCC Ltd (2001b)

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	1,3-Dimethyl-4-aminouracil (CD 19-0456)
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	Green Algae (*Scenedesmus subspicatus*)
Exposure Period	72 hours
Concentration Range Nominal	100 mg/L
Concentration Range Actual	103-104 mg/L
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	HPLC analysis with UV/VIS-detection
Remarks - Method	The study consisted of 3 replicates per test concentration and 6 of the control. Erlenmeyer flask containing the solutions were inoculated with algal suspension to give a cell density of 10000 cell per mL of test medium. The flasks were covered, incubated in a temperature controlled water bath at 22-23ºC and continuously illuminated.
RESULTS	72 hour EC_{50} > 100 mg/L
Remarks - Results	At the test concentration of 100 mg/L there was a 10% reduction in mean biomass and 3.9% reduction in mean growth when compared to the control. The appearance of the test solutions was clear throughout the study.
CONCLUSION	The EC_{50} result indicates that under the Globally Harmonised System of Classification and Labelling of Chemicals the test substance is not classified as harmful to aquatic life.
TEST FACILITY	RCC Ltd (2002p)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The water solubility, partition coefficient and adsorption constant indicate that the raw notified chemical will be slightly mobile in the environment. However, only a small amount will be disposed of to landfill thus giving very low and diffuse concentrations in any leachate.

Blooming from the pipes may occur. Thus there may be some release to environment from pipes in-situ. The removal of notified chemical from the internal surface of the pipes will probably go to sewer treatment plants and then to the aquatic compartment, while that removed from the outside surface will enter the environment, initially the soil and then the aquatic compartment. However, this release will be at very low concentrations and in a very diffuse way. The majority of the notified chemical will be bound in the PVC pipe matrix when ultimately disposed of to landfill, thus it will not be available for leaching except for the small amount that may be available due to blooming.

These parameters also indicate that the notified chemical will not bioaccumulate.

9.1.2. Environment – effects assessment

It is not expected that the notified chemical will be released directly to the water compartment. The available ecotoxicity information indicates that it is not toxic to aquatic species in any trophic level.

A predicted no effect concentration may be determined based on the algae result (EC_{50} > 100 mg/L) and applying an assessment factor of 100 (justified because acute tests are available on three trophic levels). The resultant PNEC is greater than 1 mg/L.

9.1.3. Environment – risk characterisation

None of the notified chemical will be directly released to the aquatic environment. Small amounts may ultimately reach the aquatic compartment due to blooming and leaching, but at very low and diffuse levels. The potential environmental concentration (PEC) is likely to be low, thus the PEC/PNEC ratio is likely to be much less than 1.

When used as indicated, the new chemical is not expected to present a hazard to the environment.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Categories of workers likely to be exposed to the notified chemical are those involved in transport and packaging, formulation to produce pelletised stabiliser formulation (masterbatch pellets) and PVC pipe production.

Workers exposure during transport and storage of the notified chemical in neat form or imported formulation is unlikely to occur, unless there is an accidental spillage or packaging breach.

During formulation dermal and inhalation exposure may occur when weighing and transferring the notified chemical (neat 100%), mixing, sampling and packaging. The formulation plant is expected to have local exhaust ventilation and automated processes in place. However, dermal and inhalation exposure to dust may occur as workers open the bags containing notified chemical, weigh the chemical and transfer into a mixing vessel.

Modelled Worker Exposure:

Dermal worker exposure was estimated during formulation using the software 'Estimation and Assessment of Substance Exposure' (EASE).

Dermal exposure was estimated to be 0.1-1 mg/cm^2/day notified chemical (100%), based on the following worst case scenario:

Physical state of the chemical: solid
Direct handling
Non dispersive use
Intermittent contact level

Worker exposure when generating pellets by high pressure is expected to be limited as the process is expected to be fully enclosed and automated. However, accidental spills may occur when transferring the pellets to a hopper for repacking into 20-25 bags or bulk bags. Once the blended mix is pelletised, the notified chemical is bound within the polymer matrix and not available for exposure.

During PVC pipe production, workers may come into contact with the pellets only and therefore exposure is mimimal.

Once the notified chemical is incorporated into the PVC pipe, exposure to the chemical is not expected.

9.2.2. Public health – exposure assessment

Public exposure is limited as exposure to the notified chemical is not expected once incorporated into PVC pipe.

Generated wastes from processing into PVC pipe will be incinerated and therefore direct exposure to the public is not expected.

9.2.3. Human health - effects assessment

The notified chemical is of low acute oral and dermal toxicity. It is not a skin or eye irritant and not a skin sensitiser.

The mutagenicity of the notified chemical was studied extensively. The chemical was not mutagenic to bacterial cells with and without metabolic activation. It is clastogenic without S9 to human lymphocytes in an in vitro chromosome aberration study and not mutagenic to mouse lymphoma cells with and without S9 in an in vitro cell gene mutation study. The notified chemical was not mutagenic in an in vivo micronucleus assay. The cell cycle study demonstrated that the notified chemical causes retardation of the cell cycle

Because of the limited evidence of mutagenicity (only in one invitro study), the notified chemical does not warrant classification as mutagenic or R40- possible risk of irreversible effects in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999).

The NOAEL was established as 121 mg/kg bw/day (2000 ppm) derived from a 90-day repeat dose toxicity study in rats and based on effects seen on body weight, haematology, clinical biochemistry, organ weight and pathological investigations at 10000 ppm.

Dust is expected to be generated from handling the chemical in powder form. The particle size determination indicated that particles were mainly above the inspirable fraction (180μm) in size.

9.2.4. Occupational health and safety – risk characterisation

The worst case scenario of occupational exposure is considered to be when handling neat notified chemical.

During formulation of the masterbatch pellets (10-30% notified chemical), dermal and inhalation exposure to dust may occur when opening the bags, weighing and transferring into the mixer. It is expected that the processes of mixing and transferring to the receiving hopper and pelletiser are automated and enclosed. Packing of the pellets (stabiliser product) is expected to be automated with local exhaust ventilation. Considering that the chemical is of acute low toxicity and the topical hazards are low, the risk of adverse health effects during formulation is low.

Inhalation exposure to dust may occur; however the particle size determination indicates that there are no respirable dust particles present. A dust mask, gloves and overalls should be worn by workers opening the bags, weighing and transferring neat notified chemical or pellets (stabiliser product) to avoid direct skin contact.

The estimated dermal exposure during formulation is 0.1-1 mg/cm^2/day, based on EASE model. Therefore, for a 70 kg worker with surface area for hands at 820 cm^2 and a default dermal absorption factor of 10%, systemic exposure is estimated to be 0.117-1.17 mg/kg bw/day.

The margin of exposure (MOE) was based on a NOAEL of 121 mg/kg bw/day. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Based on the above, the MOE is calculated as 1037-103.

The risk using modelled worker data is acceptable for formulation workers handling the neat notified chemical.

During end use (PVC pipe production), workers may handle the masterbatch pellets of finished pipe only, engineering controls are likely to be similar to that in the reformulation plant. The risk to the notified chemical is expected to minimal, as the notified chemical is bound within the polymer matrix. Workers should wear gloves, overalls and a dust mask if dust is generated when emptying the bags and handling the granular/pellet product.

9.2.5. Public health – risk characterisation

The risk to public health is assessed as low. After use, the notified chemical will be bound within the PVC matrix and unavailable for exposure.

10. CONCLUSIONS – ASSESSMENT LEVEL OF CONCERN FOR THE ENVIRONMENT AND HUMANS

10.1. Hazard classification

Based on the available data the notified chemical is not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio, the chemical is not considered to pose a risk to the environment based on its reported use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is Low Concern to occupational health and safety under the conditions of the occupational settings described.

10.3.2. Public health

There is Low Concern to public health when used according to instructions.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994a). It is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

11.2. Label

The label for the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994b). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical [when introduced as neat chemical]:
  - *Automated processes; local exhaust ventilation*

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical [as introduced or in the formulated product]:
  - *Gloves, overalls and dust mask*

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to

health in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Environment

- The following control measures should be implemented by the notified chemical manufacturer, the formulator and the pipe manufacturer to minimise environmental exposure during (manufacture, formulation, use) of the notified chemical:
  - Collect any spilt or surplus material and store in labelled container until disposal.

Disposal

- The notified chemical should be disposed of to landfill or by incineration.

Emergency procedures

- Spills/release of the notified chemical should be handled by containment, then collected by sweeping or other mechanical collection means and then stored in a clearly labelled container ready for disposal.

12.1. Secondary notification

The Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

Under Subsection 64(2) of the Act:
- if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

13. BIBLIOGRAPHY

BASF Aktiengesellschaft (1987a). Estimate of the potential acute hazard after single administration (determination of the LD50). BASF Aktiengesellschaft, Germany.*

BASF Aktiengesellschaft (1987b). Assessment of a possible irritating or corrosive potential to the skin. BASF Aktiengesellschaft, Germany.*

BASF Aktiengesellschaft (1987c). Assessment of a possible irritating potentil to the eye and to the eye mucosa. BASF Aktiengesellschaft, Germany.*

Ciba Specialty Chemicals Inc. (1998). Statement on Mutagenicity D19-456. Ciba Specialty Inc., Switzerland.*

Lyman WJ, Reehl WF and Rosenblatt DH (1990) Handbook of Chemical Property Estimation Methods. Environementlal Behavior of Organic Compounds. American Chemical Society, Washington, DC.
NOTOX B.V. (1997a). Evaluation of the mutagenic activity of TKA 40179 (D19-456) in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). NOTOX Project 206911, NOTOX B.V. The Netherlands.*

NOTOX B.V. (1997b). Evaluation of the ability of TKA 40179 (D19-456) to induce chromosome aberrations in cultured peripheral human lymphocytes (with independent assay) NOTOX Project 206922, NOTOX B.V. The Netherlands.*

NOTOX B.V. (1997c). Evaluation of the ability of the mutagenic activity of TKA 40179 (D19-456) in an *in* vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat). NOTOX Project 206933, NOTOX B.V. The Netherlands.*

NOTOX B.V. (1998a). Subchronic 90-day oral toxicity with TKA 40179 (D19-456) by dietary administration in the rat followed by a 28-day recovery period.. NOTOX Project 206955, Ciba Project No 974031, NOTOX B.V. The Netherlands.*

NOTOX B.V. (1998b). Micronucleus test in bone marrow cells of the mouse with TKA 40179 (D19-456). NOTOX Project 216315, NOTOX B.V. The Netherlands.*

Novartis Crop Protection AG (1998). Analysis of cell-cycle distribution of Chinese hamster cells *in vitro* by flow cytometry. Novartis Crop Protection AG, Switzerland.*

RCC Ltd (2002a). Determination of the melting point/melting range of 1,3-dimethyl-4-aminouracil (CD 19-0456). RCC Study number. 842451. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002b). Determination of the relative density of 1,3-dimethyl-4-aminouracil (CD 19-0456). RCC Study number. 842452. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002c) Calculation of the vapour pressure of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842453. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002d) Hydrolysis determination of 1,3-dimethyl-4-aminouracil (CD-19-0456) at different pH values. RCC Study number. 842469. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002e) Determination of the partition coefficient (n-octanal/water) of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842454. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002f) Expert Statement. On the adsorption coefficient for solid and sediment of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842470. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002g) Calculation of the dissociation constant of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842460. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002h). Determination of the particle size distribution of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842827. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002i). Determination of the flammability of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842457. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002j). Determination of the relative self-ignition temperature of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842458. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002k). Expert statement on the explosive properties of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842455. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002l). Expert statement on the reactivity of 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842461 Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002m). Acute dermal toxicity in rats: 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842463. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002n). Contact hypersensitivity in albino guinea pigs, maximization test: 1,3-dimethyl-4-aminouracil (CD-19-0456). RCC Study number. 842464. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2001a) Ready Biodegradation of 1,3-dimethyl-4-aminouracil (CD 19-0456) in a DOC die-away test. RCC Study number. 803417. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.

RCC Ltd (2001b) Acute Toxicity of 1,3-dimethyl-4-aminouracil (CD-19-0456) to *Daphnia magna* in a 48-hour immobilization test. RCC Study number. 803384. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.

RCC Ltd (2002o) Acute Toxicity of 1,3-dimethyl-4-aminouracil (CD-19-0456) to Zebra Fish (*Brachydanio rerio*) in a 96 hour static test. RCC Study number. 842465. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

RCC Ltd (2002p) Toxicity of 1,3-dimethyl-4-aminouracil (CD-19-0456) to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test. RCC Study number. 842467. Environmental Chemistry and Pharmanalytics Division, RCC Ltd, Switzerland.*

Vinyl Additives GmbH (1998) Determination of the water solubility at room temperature (20ºC) of 1,3-dimethyl-4-aminouracil = TKA 40179 (D 190456). Germany.*