File No: NA/784

June 2000

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

CIN 10098400

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Director
Chemicals Notification and Assessment

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FULL PUBLIC REPORT

CIN 10098400

1. APPLICANT

Kodak Australasia Pty Ltd of 173 Elizabeth St COBURG VIC 3058 has submitted a standard notification statement in support of their application for an assessment certificate for CIN 10098400.

2. IDENTITY OF THE CHEMICAL

The chemical name, CAS number, molecular and structural formulae, spectral data, details of non-hazardous impurities and details of use, formulation and release of the notified chemical have been exempted from publication in the Full Public Report and the Summary Report.

Marketing Name:	CIN 10098400
Method of Detection and Determination:	can be detected by HPLC and characterised by UV/visible, infrared (IR) and ^{1}H nmr spectroscopy (1D and 2D)
Molecular Weight:	782.27

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	off white solid
Melting Point:	144.5 – 161.0°C (OECD TG 102)
Boiling Point:	decomposes above 246°C at 6.7 kPa (OECD TG 103)
Specific Gravity:	1.2767 at 20°C (OECD TG 109)
Vapour Pressure:	$< 1.3 \times 10^{-7}$ kPa at 25°C (OECD TG 104)
Water Solubility:	< 0.026 mg/L at 25°C (OECD TG 105) (see comments below)

Particle Size:	Size Range (μm)	Mass %
Inspirable range:	< 38	0.593
	38 - 53	0.074
	53 - 75	0.915
	75 - 106	1.335
	106 – 150	3.561
	150 - 212	4.006
	212 - 300	4.402
	300 - 420	4.377
	420 - 595	4.154
	595 - 850	4.946
	850 - 1190	5.762
	1190 - 1680	7.888
	1680 - 2360	9.372
	> 2360	48.566
	median size 2267 μm	

Partition Co-efficient (n-octanol/water):	log P_{ow} > 5.19 (OECD TG 107) (see comments below)
Hydrolysis as a Function of pH:	$T_{1/2}$ at pH 4.0 not determined (see comments below) $T_{1/2}$ at pH 7.0 not determined (see comments below) $T_{1/2}$ at pH 9.0 652 hours
Adsorption/Desorption:	K_{oc} range 590-5371 (see comments below) (OECD TG 106)
Dissociation Constant:	not determined (see comments below)
Flash Point:	not applicable for solids of low vapour pressure
Flammability Limits:	not highly flammable; combustible (84/449 EEC, A.10)
Autoignition Temperature:	no self-ignition to 400°C (84/449 EEC, A.16)
Explosive Properties:	not explosive (84/449 EEC, A.14)
Reactivity/Stability:	not oxidising (84/449 EEC, A.17); not expected to be highly reactive under normal environmental conditions

3.1 Comments on Physico-Chemical Properties

Water solubility was determined by the column elution method and using High Performance Liquid Chromatography (HPLC) for detection. Distilled water was circulated through the columns at a rate of approximately 10 mL/min and aliquots were collected between 0 and 96 h. The solubility of the substance was determined from the samples taken between 66.5 and 96.25 h. However, it was found that while possible to determine the presence of the compound in water, the size of the peak in the chromatogram was small, and below the quantitative detection limit of the equipment used (<0.026 mg/L).

The potential of the notified chemical to undergo hydrolytic degradation in an aquatic environment could not be determined in laboratory tests at pH 7 due to the limited solubility of the chemical in a preliminary test at 50°C in pH 7 buffer. The estimated half-life of the chemical for the pH 4 test system was not determined as < 10 % drop in concentration was observed during the preliminary test at 119 h at 50°C. The results of the preliminary test for the pH 9 test system indicated that test 3 at 60, 70 and 80°C should be performed. A linear regression analysis was used to calculate the observed rate constant (k_{obs}) from which the half-life of the chemical was calculated at each temperature. An Arrhenius plot of the natural logarithm of k_{obs} versus 1/T was then generated. The $t_{1/2}$ was 41 h at 50°C, 48 h at 60°C, 14 h at 70°C and 4.3 h at 80°C.

No data on the dissociation constant could be submitted as the pK_a of the notified chemical could not be determined. The compound does not contain any highly acidic or basic groups capable of dissociating in water, so dissociation constant data is not considered necessary.

Experimental determination of the n-octanol/water partition coefficient was made by the shake-flask method. Test systems were prepared by diluting a stock solution of the notified chemical in n-octanol and distilled water. The test tubes were shaken for 30 minutes, centrifuged and aliquots of the water and n-octanol layers were removed for analysis by HPLC/UV. It was observed that the water and n-octanol layers were clear and colourless. The mass balance analysis of the test systems determined that the recovered amount of the chemical was between 139 and 145 % of the test substance introduced into each test system. Use of the HPLC method (OECD TG 117) may have provided a more accurate estimate, which in turn could have allowed a better calculation of water solubility.

Adsorption data was derived using the screening part of OECD TG 106 (North, 1999). The three soil types were mixed with the test solution (1.178 mg/L notified chemical in 5 % DMF in 0.01 M NH_4OAc), mixed for 16 hours at 24°C, centrifuged and analysed using HPLC/UV.

Desorption data was derived using the soil samples from the adsorption phase. 20 mL of 5 % DMF in 0.01 M NH_4OAc was added to each sample, mixed for 17 h at 24.5°C, centrifuged and analyzed by HPLC/UV (desorption wash 1). The same process was again repeated on the same samples with the mixing phase lasting for 21.5 h (desorption wash 2).

Results are as follows:

Soil Type	pH	Organic Carbon %	Mean % Adsorbed	Mean % Desorbed	Mean % Retained	Mean K	Mean K_{oc}
Spodosol	4.7	2.4	69.8	20.7	79.3	14.2	590
Alfisol	6.5	3.0	>91.4	17.3	82.7	62.3	2078
Entisol	7.5	1.2	>91.4	17.2	82.8	64.4	5371

4. PURITY OF THE CHEMICAL

Degree of Purity: 98.4 %

Hazardous Impurities: one hazardous impurity, a derivative of 2-chloro-p-phenylenediamine, was identified as being responsible for the observed results in the *Salmonella typhimurium* point mutation test (see below); HPLC tests indicated that no impurity was present at greater than 0.4 %

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

Additives/Adjuvants: none

5. USE, VOLUME AND FORMULATION

The notified chemical will be used in the manufacture of photographic film and paper.

The notified chemical will not be manufactured in Australia. It will be imported as a powder in plastic bags inside cardboard cartons, each bag containing 6 kg of notified chemical. The import volume for the notified chemical is estimated to be approximately 3 tonnes per annum during the first five years of importation.

6. OCCUPATIONAL EXPOSURE

Transport and Storage
Transport and storage workers are not likely to be exposed to the notified chemical except in the case of an accident involving damage to the packaging. No details of occupational exposure were provided by the notifier.

Formulation
The appropriate amount of the notified chemical, in solid form, will be weighed and added to mix tanks with other substances to form gelatin dispersions (< 1 % notified chemical) in multi-batch runs, with 552 kg batch size, once per week. Weighing and addition to the mix tanks will be performed manually. Weighing will take approximately 30 minutes per batch and addition of the notified chemical will take approximately 1 minute per batch. Dermal

contact would be the main route of exposure for workers at the mix tank site. However, inhalation and eye exposure to the solid form of the notified chemical may also occur because weighing and adding to the mix tank is an open process.

Weighing of the notified chemical and addition to the mix tank will be conducted under local exhaust ventilation. Workers handling the dry powder are to wear company provided overalls, safety glasses, disposable vinyl gloves, and a disposable particle mask.

The notifier indicates that 12 operators will be involved in producing the gelatin dispersions.

The gelatin dispersion will be bagged and stored in a cold room up to several weeks prior to use. At the melt tank site, the gelatin dispersion and other ingredients will be added to melt tanks, further diluting the notified chemical. A sample of the melt will be taken for laboratory testing. The occupational exposure would be predominantly by dermal contact during the addition of gelatin dispersion into the melt tanks. Workers are to wear overalls, safety glasses and gloves (as described above) during this process. The melt dispersion will then be pumped to automated processing equipment, where the notified chemical will be incorporated into photographic films and paper. Intermittent dermal exposure to the notified chemical is also possible during cleaning of automated processing equipment.

The notifier indicates that 16 operators and 4 technicians will be involved in handling the gelatin dispersions.

End Use
The notifier indicates that the notified chemical will be under overcoat layers in the finished articles, and no exposure of end users such as photographers and minilab operators is likely.

7. PUBLIC EXPOSURE

The notified chemical will be used only within an industrial environment prior to incorporation in photographic film and paper. These will be sold to the public and will be widely available in the public domain. However, once incorporated onto photographic film or paper, the gelatin dispersion containing the notified chemical will reside beneath several overcoat layers, which limits the possibility of dermal contact.

8. ENVIRONMENTAL EXPOSURE

8.1 Release

Some chemical is likely to remain in the empty bags. The company estimates that 19 kg per year of the chemical will be left as residues when the import containers are emptied and 1.5 kg per year will be trapped in the filters used in the dust extraction equipment. These residues will be disposed to landfill as will any reject gelatin dispersion (< 0.1 % of import volume). The company also indicated that around 1.8 % of the chemical may be released in various process liquors, and that this would be released to the sewer system, and discharged to the sea after treatment. This amounts to an estimated total release of around 77 kg each year of which 54 kg will be to the sewers and 23 kg to landfill.

The company states that any rejected finished articles coated with the melt containing the notified chemical will be sent to the United States for smelting to recover the silver.

Most of the chemical is expected to be retained in the photographic emulsion and would consequently be dispersed widely through use in minilabs throughout Australia. The notifier claims that there will be no release of the chemical during the minilab processing as it will remain bound to the paper. Eventual disposal of photographs and negatives is likely to be through deposition into landfill where very slow release could be expected as the photographs and the emulsion become degraded. Some photographs and negatives may be incinerated, which would destroy the chemical, producing water vapour and oxides of nitrogen and sulphur and hydrogen chloride.

8.2 Fate

The notifier included reports on a Biochemical Oxygen Demand (BOD) (Foley, 1999a) and a Chemical Oxygen Demand (COD) (Foley, 1999b) determination. The BOD of the chemical could not be determined due to the insolubility of the chemical in water. The COD was measured in compliance with "OECD Principles of Good Laboratory Practice", {C(97) 186(Final)], Annex 2 and found to be1.84 g COD/g test substance.

The substance was examined for biodegradation potential (Berlinger, 1998) using EEC Directive 92/69, Part C.4-C (Modified Sturm Test), and OECD Test Guideline 301B (substance added directly to test carboys due to sparing solubility). Over the 28 day test, biodegradation reached 9 % and 3 % in the two replicates, indicating not readily biodegradable under the conditions of the test; the control solution containing sodium benzoate reached 78% biodegradation over the 28 day test period.

The very low water solubility and high value for the n-octanol/water partition coefficient indicate that once released to the water compartment, the compound would very likely become strongly associated with aquatic sediments. While the compound is not biodegradable under aerobic conditions, once adsorbed into aquatic sediments in anaerobic environments it may be slowly degraded through various biological and abiotic processes. The degradation products are likely to be water, methane and oxides of carbon. Any material disposed of into landfill (eg residues in empty bags) is also expected to become associated with the organic component of soils, and may also be slowly degraded over time.

In the absence of additional test data on biodegradation rates under both aerobic and anaerobic conditions, the available data indicates that once released the compound is likely to be persistent in the environment. This may have implications for bioaccumulation potential (see further below).

Discarded photographs and film negatives would most probably be placed into landfill where the chemical is expected to be slowly released as the film and emulsion are degraded. It is expected that released compound would become associated with the organic component of the soil, and would be slowly destroyed as indicated above. Some photographs and negatives may be incinerated which would result in complete destruction of the compound with formation of oxides of nitrogen and sulphur and hydrogen chloride.

The compound has very low water solubility, a large value for the n-octanol/water partition coefficient, and is not susceptible to rapid biodegradation. Connell (Connell, 1990) indicates

that this combination of physico-chemical attributes gives chemicals a high potential for bioaccumulation. Connell also points out molecular weight is important, and that compounds having molecular weights in excess of 600 g/mol have attenuated potential for bioaccumulation. The present compound has a molecular weight of greater than 600 g/mol, and this presumably mitigates the potential for bioaccumulation.

The chemical will largely be confined to the sewer system, with very little released to natural waters.

9. EVALUATION OF TOXICOLOGICAL DATA

All toxicity studies were performed using the pure notified chemical, identified as 76AQZ.

9.1 Acute Toxicity

Summary of the acute toxicity of CIN 10098400

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50}>2000 mg/kg	(Shepard, 1999c)
acute dermal toxicity	rat	LD_{50}>2000 mg/kg	(Jessup, 1999)
skin irritation	rabbit	non-irritating	(Shepard, 1999a)
eye irritation	rabbit	slight irritant	(Shepard, 1999b)
skin sensitisation	guinea pig	non-sensitising	(Shepard, 1999d)

9.1.1 Oral Toxicity (Shepard, 1999c)

Species/strain:	rat/Sprague Dawley
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	gavage; single dose of 2000 mg/kg of test substance as a 20 % (w/v) suspension in 0.5% carboxymethylcellulose vehicle
Test method:	OECD TG 401
Mortality:	no deaths were recorded during the study period
Clinical observations:	these were limited to discoloured (light brown) faeces from all animals the day following dosing
Morphological findings:	no treatment-related changes were observed at necropsy

Comment:	all animals gained weight during both weeks of the observation period
LD_{50}*:*	> 2000 mg/kg
Result:	the notified chemical was of very low acute oral toxicity in rats

9.1.2 Dermal Toxicity (Jessup, 1999)

Species/strain:	rat/Sprague Dawley
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	single dose of 2000 mg/kg test substance, moistened in water, was administered under occlusive conditions on the dorsal skin for 24 hours
Test method:	OECD TG 402
Mortality:	no deaths were recorded during the study period
Clinical observations:	no clinical signs of toxicity were observed
Morphological findings:	no treatment-related changes were observed
Comment:	all animals gained weight during both weeks of the observation period
LD_{50}*:*	> 2000 mg/kg
Result:	the notified chemical was of low dermal toxicity in rats

9.1.3 Inhalation Toxicity

No inhalation study was provided by the notifier, due to the physical form of the chemical (large particles with a very low respirable fraction) and its mode of use. As the notified chemical has a very low inspirable fraction (< 0.6 %), the argument was accepted for the purposes of the assessment.

9.1.4 Skin Irritation (Shepard, 1999a)

Species/strain:	rabbit/New Zealand White
Number/sex of animals:	3 (sex unspecified)
Observation period:	3 days

Method of administration: single dose of 0.5 g test substance, moistened in water, was administered under occlusive conditions on the dorsal skin for 4 hours

Test method: OECD TG 404

Comment: no irritant skin lesions were noted during the 72-hour observation period; all individual dermal reaction scores were zero

Result: the notified chemical was non-irritating to the skin of rabbits

9.1.5 Eye Irritation (Shepard, 1999b)

Species/strain: rabbit/New Zealand White

Number/sex of animals: 6 (sex unspecified)

Observation period: 7 days

Method of administration: a single dose of 0.1 gm of test substance was placed in the conjunctival sac of the right eye of all animals; the substance was immediately washed from the eyes of three of the animals, while the eyes of the other three treated animals remained unirrigated; the untreated eye was used as control

Test method: OECD TG 405

Draize scores (Draize, 1959):

	Time after instillation											
Animal	***1 hour***			***1 day***			***2 days***			***3 days***		
Cornea	all Draize scores were zero											
Iris	all Draize scores were zero											
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	1[1]	1	1	2	2	2	2	1	0	1	0	0
2	2	0	1	1	0	0	0	0	0	0	0	0
3	2	1	2	2	1	2	2	0	0	1	0	0
4i	1	0	0	0	0	0	0	0	0	0	0	0
5i	1	0	0	0	0	0	0	0	0	0	0	0
6i	1	0	0	0	0	0	0	0	0	0	0	0

[1] see Attachment 1 for Draize scales
r = redness c = chemosis d = discharge i = irrigated eye

Comment:	all ocular effects had resolved by the 7 day observation
Result:	the notified chemical was slightly irritating to the eyes of rabbits

9.1.6 Skin Sensitisation (Shepard, 1999d)

Species/strain:	guinea pig/Crl:(HA)BR VAF/Plus
Number of animals:	20 test animals; 10 control animals
Induction procedure:	day 0 for the test group, three pairs of intradermal injections were made to each animal, flanking the midline: 1. 0.1 mL of Freund's Complete Adjuvant (FCA) emulsion with distilled water (1:1) 2. 0.1 mL of 3 % test substance in corn oil 3. 0.1 mL of 3 % test substance in FCA emulsion with distilled water (1:1) for control animals, the test substance was replaced with corn oil day 5 irritation was induced at the injection site for both the test and control group by application of 0.5 mL 10 % sodium lauryl sulphate in petrolatum day 6 for the test group, a patch with 0.5 gm of neat test substance moistened in water was applied to the injection site, secured with a bandage, and left in place for 48 hours for the control group, distilled water only was used in this induction phase
Challenge procedure:	day 20 a patch with 0.25 gm of neat test substance, moistened with water, was applied to the left flank of all animals, secured with bandage, and left in place for 24 hours; vehicle only (distilled water) was applied to the right flank; dermal reactions were scored at 24 and 48 hours after challenge exposure
Test method:	OECD TG 406; Magnusson & Kligman Maximisation Test
Comment:	no dermal responses were noted after the challenge dose for either the control or test animals

Result:	the notified chemical was non-sensitising to the skin of guinea pigs

9.2 Repeated Dose Toxicity (Gearhart, 1999)

Species/strain:	rat/Sprague Dawley
Number/sex of animals:	5/sex/group
Method of administration:	diet *ad libitum*
Dose/Study duration:	15.0, 4.5, 1.5 or 0.0 mg/g, days 1 to 14 17.0, 4.5, 1.5 or 0.0 mg/g, days 15 to 28 males 0, 104.6, 296.8,1124.7 mg/kg/day females 0, 115.2, 346.9, 1330.6 mg/kg/day (high dose animals are referred to as 15 mg/g in the discussion below)
Test method:	OECD TG 407

Clinical observations:
No deaths were recorded during the study.

One male rat from the 4.5 mg/g group had minor reductions in amount of faeces on one day. Minor nasal porphyrin discharges were observed for one 1.5 mg/g female and one control male. In addition, one 15 mg/g male had a malocclusion of the teeth with accompanying porphyrin discharges from the eyes and nose, and a swollen muzzle. No significant differences for any of the groups were observed in the functional observational battery.

There were no significant differences in mean body weights among any of the groups.

Clinical chemistry/Haematology
Significant differences in clinical chemistry parameters were limited to lower mean phosphorus concentrations for the 15 mg/g males compared with controls. Changes in haematology values consisted of lower mean corpuscular haemoglobin concentrations for the 15 mg/g and 1.5 mg/g female groups. Changes in cell morphology were limited to minimal to minor poikilocytosis (presence of abnormally shaped erythrocytes), which was observed for two to four animals of each group, including controls, and minimal anisocytosis (presence of erythrocytes with excessive variation in size), which was observed for one 15 mg/g female.

Pathology:
Organ weights
Mean relative kidney weights were significantly lower for the 1.5 mg/g males compared with controls. Mean absolute spleen weights were significantly higher for the 1.5 and 4.5 mg/g females compared with controls, and relative spleen weights were higher for the 4.5 mg/g females.

Gross pathology
Gross lesions at necropsy were minimal to moderate thymic haemorrhage or discolouration, which was observed for one or two animals of each group, minor hydrometra (watery fluid) of the uterus which was observed for one 15 mg/g female rat and a minor haematoma on the bones of the skull in one 15 mg/g male. No other gross lesions were observed.

Histopathology
Complete histopathological examinations were only carried out for the high dose (15 mg/g) and control animals.

All 15 mg/g males showed minimal to mild hepatocellular vacuolation, compared with only two controls. Ultimobranchial cleft cysts in the thyroid gland were seen for three 15 mg/g males compared with no controls, while for females this observation was made for three controls and two 15 mg/g animals. Prostatitis was observed in three 15 mg/g males, compared with no controls. Interstitial pneumonitis was observed in two males and one female of each of the 15 mg/g group and control group. Mononuclear cell infiltrates within the liver were observed for all 15 mg/g females, compared with no controls, but in the males this observation was made for three controls and four 15 mg/g animals. One 15 mg/g male had a focus of epicarditis composed primarily of lymphocytes.

The lesions from the various groups were considered to be incidental due to their limited incidence or occurrence in both high dose and control animals, with no clear increases in incidence in the high dose groups, or as they are common background findings in rats of this age and strain, with the differences in incidence related to the small sample size.

Comment:
The changed organ weights were not considered toxicologically significant by the study authors, as no similar findings were made for the high dose groups. Differences in clinical chemistry values and haematology parameters were considered to be within the normal range for animals of this strain and age. All lesions were considered to be incidental due to their limited incidence or occurrence in both high dose and control animals, with no clear increases in incidence in the high dose groups, or as they are common background findings in rats of this strain and age. Changes in red blood cell morphology were also considered by the authors to be within historical control ranges. Historical control data was not provided in the study report.

Result:
Based on the absence of significant findings at any dose tested, the notified chemical was found in this study to have a No-Observed-Adverse-Effect-Level (NOAEL) of 1124 mg/kg/day (15 mg/g to 17 mg/g in diet).

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay (Lawlor, 1999)

Strains:	*Salmonella typhimurium* TA1535, TA1537, TA98 and TA100; *Escherichia coli* WP2*uvr*A(pKM101)

Concentration range:	0, 33.3, 100, 333, 1000, 2500 and 5000 μg/plate, dissolved in dimethylsulphoxide (DMSO)
Metabolic activation:	10 % rat liver S9 fraction (Aroclor 1254-induced) in standard cofactors
Positive controls:	with S9: 2-aminoanthracene TA98, TA100, TA1535, TA1537: 2.5 μg/plate WP2*uvr*A: 5 μg/plate without S9 TA98: 2-nitrofluorene 1.0 μg/plate TA100,TA1535: sodium azide 2.0 μg/plate TA1537: ICR-191 2.0 μg/plate WP2*uvr*A: 4-nitroquinoline-N-oxide 2 μg/plate
Test method:	OECD TG 471 (plate incorporation method)
Comment:	each experiment, in the presence and absence of S9, was repeated once and all concentrations were tested in triplicate precipitation was observed at and above 1000 μg/plate and did not allow evaluation of the background lawn, but did not interfere with scoring of revertant colonies under the conditions of the study, the test substance caused an increase of 14.9 fold and 17.4 fold in the initial and confirmatory assays, respectively, in TA98 in the presence of metabolic activation; a clear dose response was observed above 1000 μg/plate; no increase was observed in the absence of metabolic activation; 1.9 fold and 1.7 fold increases were observed for TA 100 in the presence of metabolic activation in the initial and confirmatory assays, respectively with again no increase in the absence of metabolic activation no substantial increases in revertant colony numbers over control counts at any concentration in either the presence or absence of rat liver microsomal enzymes were observed for the other strains all positive and negative controls responded appropriately and all criteria for a valid study were met
Result:	the notified chemical was considered to be mutagenic under the conditions of the assay in the presence of exogenous metabolic activation

9.3.2 Chromosome aberration test in Chinese hamster ovary (CHO) cells *in vitro* (Murli, 1999)

Cells:	Chinese Hamster Ovary (CHO) cells
Metabolic activation:	1.5 % rat liver S9 fraction (Aroclor 1254-induced) in standard cofactors
Positive controls:	With S9: 5 and 10 μg/mL cyclophosphamide Without S9: 0.75 and 1.5 μg/mL mitomycin C
Experimental design:	The test substance was dissolved in DMSO Experiment 1. cells were treated for 3 hours and harvested 20 hours from initiation of treatment; doses 0.0868, 0.124, 0.247, 0.493, 0.985, 1.97, 3.93, 7.85, 15.7, 31.3, 62.5, 125, 250, 500 and 1000 μg/mL; doses analysed for chromosomal aberrations were 62.5, 125, 250 and 1000 μg/mL, and 62.5, 125, 500 and 1000 μg/mL in the absence and presence of S9, respectively reductions in mitotic index of 42 % and 47 % were observed at the highest dose evaluated in the absence and presence of S9, respectively Experiment 2. cells were treated for 17.8 hours (-S9) and 3.0 hours (+S9) and harvested 21 hours from initation of treatment; doses 7.85 and 15.7 μg/mL in the absence of S9 and 31.3, 62.5, 125, 250, 500 and 1000 μg/mL both in the absence and presence of S9; culture test concentrations analysed for chromosomal aberrations were 62.5, 250, 500 and 1000 μg/mL in both cases reductions in mitotic index of 44 % and 26 % were observed at the highest dose evaluated in the absence and presence of S9, respectively
Test method:	OECD TG 473
Comment:	the test substance did not induce any significant or dose-related increases in the frequency of cells with aberrations in either the initial or the confirmatory experiments all positive and negative controls responded appropriately and all criteria for a valid study were met
Result:	the notified chemical was considered to be non-clastogenic

under the conditions of the study

9.4 Overall Assessment of Toxicological Data

The notified chemical was of very low acute oral toxicity (LD_{50} > 2000 mg/kg) and low acute dermal toxicity (LD_{50} > 2000 mg/kg) in the rat. The notified chemical was non-irritating to rabbit skin. It produced slight irritation in the eyes of rabbits with conjunctival effects persisting beyond 3 days. There was no evidence of sensitisation in an adjuvant type study with guinea pigs. No acute inhalation toxicity study report was provided by the notifier.

In a 28 day repeat dose oral (dietary admixture) toxicity study in rats, lesions from the various groups were considered to be incidental due to their limited incidence or occurrence in both high dose (1124 mg/kg/day for male rats and 1330 mg/kg/day for female rats) and control animals, with no clear increases in incidence in the high dose groups, or as they are common background findings in rats of this age and strain, with the differences in occurrence related to the small sample size. Based on the absence of significant findings at any dose tested, the results of the study established a NOAEL of 1124 and 1330 mg/kg/day (the highest doses tested) for male and female rats, respectively.

In genotoxicity studies, the notified chemical was mutagenic in *Salmonella typhimurium* TA98 in the presence of metabolic activation, with 14.7 fold and 17.9 fold increases in the number of revertants. Small increases in the number of revertants were also seen for TA100 in the presence of metabolic activation. The notifier indicated that the increases were probably due to the presence of an impurity, a derivative of 2-chloro-p-phenylenediamine, which is much more water soluble than the notified chemical. The notifier states that 2-chloro-p-phenylenediamine has also been shown to be positive in the bacterial point mutation test (Ames test) with similar strain specificity to that observed for the notified chemical. The notified chemical did not induce an increased incidence of chromosomal aberrations in Chinese hamster ovary cells *in vitro*.

The notifier provided an assessment of the toxicokinetics of the notified chemical. It was concluded that there was no evidence, based on the results of the 4-week repeat dose oral study, the acute oral toxicity study and the acute dermal toxicity study, that the notified chemical is absorbed across the intestinal mucosa or skin.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The notifier supplied the following ecotoxicity data in support of the application. The test data were generated according to OECD protocols.

Test	*Species*	*Results (nominal)*
Acute Toxicity to Fish [OECD 203]	**Fathead minnow *Pimephales promelas***	LC_{50} (96 h) > 0.42 mg/L
Acute Immobilisation to Fresh water invertebrates [OECD 202]	**Daphnia magna**	EC_{50} (48 h) > 0.43 mg/L
Inhibition of Algal growth [OECD TG 201]	*Selenastrum capricornutum*	E_bC_{50} (72 h) > 0.54 mg/L

Respiration Inhibition of Activated Sludge Bacteria [OECD TG 209]	Activated sludge bacteria	EC_{50} (3 h) > 1000 mg/L	

Fish
Two replicate solutions containing 1.0 mg/L CIN 10098400 were prepared by adding the appropriate volume of a stock solution of the chemical in N,N-dimethylformamide to 20 L of dilution water (Light, 1999c). The vessels were stirred for 24 h using a Teflon stir bar and replicate A appeared very slightly cloudy in appearance whilst replicate B was clear and colourless throughout the test. Following preparation of the test media, 7 fathead minnows were added to each of the three vessels, and the general health of these animals monitored over a four day (96 hour) period. As a control, 7 fish were also placed in a separate test vessel to which no test compound had been added. Temperature was maintained at 20-21°C, pH values were between 8.2 and 9.0 and dissolved oxygen levels were between 7.6 and 8.7 mg/L.

No mortality or aberrant behaviour was observed in any of the test specimens or in the control fish. From these observations, it was concluded that the new compound is not toxic to this species up to the limits of its water solubility. This was determined to be 0.42 mg/L in this test (geometric mean of analysed solutions at t=0 and 96 h, n=2).

Invertebrates
An acute toxicity test of new chemical against *Daphnia magna* was conducted using a static methodology (Light, 1999b). As with the fish test, the media was made up by adding the appropriate volume of a stock solution of the chemical in N,N-dimethylformamide to two 20 L glass vessels of dilution water. Aliquots were then transferred to the 250 mL test vessels.

Ten daphnia were placed in the duplicate test vessels. The general behaviour of the animals in the test and control vessels was monitored over a 48 hour test period. Temperature was maintained at 21°C, pH values were between 8.5 and 8.6 and dissolved oxygen levels were between 8.5 and 8.7 mg/L.

No immobility or mortality was observed in the test media or control solutions throughout the test. Consequently it was concluded that the new compound is not toxic to *Daphnia magna* up to the limits of its water solubility. This was determined to be 0.43 mg/L in this test (geometric mean of analysed solutions at t=0 and 48 h, n=2).

Algae
Due to the low solubility of the notified chemical in water a semi-stable suspension prepared at a concentration of 1 mg/L was used as the test media (Light, 1999a). Throughout the study, the flasks were shaken at 100 rpm, the temperature was maintained at 24°C and the pH ranged from 7.30 to 7.83. Observations were made at 0, 24, 48 and 72 hours.

No inhibition of biomass or algal growth rates was observed for the controls or any of the test media. From the results of this test it was concluded that the new compound is not toxic to this species of green algae (*Selenastrum capricornutum*) up to the limits of its water solubility (0.54 mg/L geometric mean of analysed test cultures at t=0).

Sewage Bacteria

The 3 hour test was performed using activated sludge from a domestic waste water treatment plant (Berlinger, 1999). The sludge was exposed to five concentrations (25, 50, 100, 500 and 1000 mg/L) of the notified chemical. The respiration rate was measured following the 3 hour exposure period, and compared with that in a control vessel. None of the samples indicated any significant inhibition of bacterial respiration compared with the controls, and it was concluded that the new chemical is not toxic to sewage bacteria up to a nominal concentration of 1000 mg/L. However, very little of this may be expected to have been in solution.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The notified chemical is not considered to pose a hazard to the environment when used as a component of photographic emulsions in the manner indicated by the notifier.

As a result of the disposal of industrial wastes from the production of photographic emulsion, it is estimated that up to 54 kg of the chemical could be released into the Melbourne sewage system each year.

Total influent to the Werribee sewage treatment plant is around 500,000,000 litres per day (180×10^9 L per year), and consequently the Predicted Environmental Concentration (PEC) of the compound in the sewage is then 54 (kg)/180×10^9 (L) = 0.3 μg/L.

The chemical is not toxic to those species of fish, daphnia or algae against which it has been tested up to the limits of its water solubility. Similarly, the new compound does not inhibit the respiration of sewage bacteria. The PEC value is much lower than the ecotoxicity data values for the EC_{50} of fish, daphnia, algae and sludge tested and a wide safety margin appears to be present for this chemical in its predicted use pattern.

The chemical is not readily biodegradable or susceptible to chemical hydrolysis, and once released it may persist in the environment. Due to the low water solubility and high n-octanol/water partition coefficient, most of the chemical released to the sewer in this manner is expected to become associated with the aquatic sediments. The compound may be persistent in the environment so its concentration in the sewer sediments may increase with time. However, most of the chemical released to the sewer system would be expected to stay in the sewer lines or adsorb to pasture/soil when land farmed at Werribee Treatment Farm.

Up to 0.1 % (3 kg) of the notified chemical may be disposed of to landfill as reject gelatin dispersion. In addition, approximately 20.5 kg per year of the compound is expected to remain as residues in the empty bags and air filters used in the dust extraction system and disposed of similarly. Chemical released from these sources will become associated with the organic component of soils and sediments, and is not expected to be mobile.

Most of the chemical is expected to be retained in the photographic emulsions of film negatives and photographs, which are likely to be eventually discarded into landfill. Here the chemical is expected to be slowly released as the photographs degrade, and will then become associated with the organic component of soils. Some old photographs may be incinerated which will completely destroy the compound with production of water vapour and oxides of nitrogen and sulphur and hydrogen chloride.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The notified chemical does not meet the criteria for classification as a hazardous substance according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999).

The acute oral toxicity of CIN 10098400 is very low (LD_{50} > 2000 mg/kg) and the acute dermal toxicity is low (LD_{50} > 2000 mg/kg). It is not an irritant to the skin of rabbits, but is a slight irritant to rabbit eyes. It was not a skin sensitiser in guinea pigs in an adjuvant type test.

In genotoxicity studies, the notified chemical was mutagenic in *Salmonella typhimurium* TA98 in the presence of metabolic activation. The notifier indicated that the increases were probably due to the presence of an impurity, a derivative of 2-chloro-p-phenylenediamine, which is much more water soluble than the notified chemical. The notified chemical did not induce an increased incidence of chromosomal aberrations in Chinese hamster ovary cells *in vitro*.

The major hazards from acute exposure relate to the eye irritant effects and from exposure to the impurity identified as being responsible for the effects observed in the bacterial point mutation test.

For longer-term systemic effects, in a 28 day feeding study in rats, no treatment related effects were observed for any of the doses tested. Based on the absence of toxicologically significant findings at any dose, the NOAEL was found to be 15 mg/g (the highest dose tested; equal to 1124 mg/kg/day for males and 1330 mg/kg/day for females).

Occupational Health and Safety

Occupational exposure to the notified chemical can be divided into exposure to the powdered solid, the gelatin dispersions, and the finished photographic film and paper. The dust includes a low proportion (5.5 %) in the inspirable range, and less again (< 0.6 %) within the respirable range, and therefore the potential hazard by inhalation is expected to be low. Workers will handle the powdered solid for short periods during weighing and addition to the mix tanks where the gelatin dispersion is produced. Exposure may occur many times throughout the year. There is a risk of eye irritation on acute exposure to dust from the chemical.

The risk of adverse health effects will be further reduced by local exhaust ventilation during the processes which involve handling the powdered solid. The wearing of overalls, protective gloves, glasses and respiratory protection while weighing and mixing the powdered solid will also be required. Disposable gloves should not be used.

The handling of the gelatin dispersions, containing less than 10 % notified chemical, is a potential hazard by dermal exposure, particularly during cleaning of equipment. Care should be taken to avoid dermal exposure, particularly as the impurity which was identified as being responsible for the results of the bacterial point mutation test is much more soluble in water than the notified chemical, and the toxicokinetic analysis indicating low dermal absorption does not apply to this impurity. Standard procedures require the use of gloves, overalls and protective glasses by workers handling the gelatin dispersions. After incorporation in articles,

the potential hazard should be negligible as the notified chemical will be beneath several overcoat layers.

Public Health
Photographic film and/or paper containing the notified chemical will be sold to the public, consequently there will be widespread availability in the public domain. Once incorporated onto photographic film and paper, the gelatin dispersion containing the notified chemical will reside beneath several overcoat layers, limiting the possibility of dermal contact. Consequently the potential for public exposure to the notified chemical during all phases of its life cycle is low and the notified chemical is not expected to pose a significant hazard to public health when used in the proposed manner.

13. RECOMMENDATIONS

To minimise occupational exposure to CIN 10098400 the following guidelines and precautions should be observed:

- Safety goggles, chemical resistant industrial clothing and footwear and impermeable gloves should be used during occupational use of the notified chemical; disposable gloves should not be used;
- 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.

Guidance in selection of goggles may be obtained from Australian Standard (AS) 1336 (Standards Australia, 1994) and Australian/New Zealand Standard (AS/NZS) 1337 (Standards Australia/Standards New Zealand, 1992); for industrial clothing, guidance may be found in AS 2919 (Standards Australia, 1987) and AS 3765.2 (Standards Australia, 1990); for impermeable gloves or mittens, in AS 2161 (Standards Australia/Standards New Zealand, 1998); for occupational footwear, in AS/NZS 2210 (Standards Australia/Standards New Zealand, 1994).

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

16. REFERENCES

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Attachment 1

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