File No: NA/761

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**NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME**

# FULL PUBLIC REPORT

## ORACET Orange LGP

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Director
Chemicals Notification and Assessment

# FULL PUBLIC REPORT

## ORACET Orange LGP

## 1. APPLICANT

Ciba Specialty Chemicals of 235 Settlement Rd., THOMASTOWN, VIC 3074 has submitted a standard notification statement in support of their application for an assessment certificate for ORACET Orange LGP.

## 2. IDENTITY OF THE CHEMICAL

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

| | |
|---|---|
| **Marketing Name:** | ORACET Orange LGP |
| **Other Names:** | Solvent Orange CG 33-0424<br>C.I. Solvent Orange 114 |
| **Method of Detection and Determination:** | UV/visible spectrophotometry<br>Infrared spectrometry<br>$^{1}H$ nmr spectrometry<br>$^{13}C$ nmr spectrometry<br><br>Reference spectra have been provided by the notifier. |

## 3. PHYSICAL AND CHEMICAL PROPERTIES

Tests were performed according to EEC/OECD test guidelines at facilities complying with OECD Principles of Good Laboratory Practice except where a test regarded of at least equivalent status has been identified.

| | |
|---|---|
| **Appearance at 20°C and 101.3 kPa:** | Odourless orange/red powder |
| **Melting Point:** | 250°C |
| **Specific Gravity:** | 1.160 |
| **Vapour Pressure:** | $9 \pm 1 \times 10^{-6}$ kPa at 20°C |

| | |
|---|---|
| **Water Solubility:** | < $4.52 \times 10^{-3}$ mg/L at 19.5°C |

**Particle Size:**

| Size Range (μm) | Mass % |
|---|---|
| < 10 | 0.1 |
| 10 – 20 | 0.1 |
| 20 – 50 | 0.8 |
| 50 – 100 | 4.5 |
| 100 – 250 | 13.2 |
| > 250 | 81.3 |

| | |
|---|---|
| **Partition Co-efficient (n-octanol/water):** | log $P_{ow}$ > 6.2 |
| **Hydrolysis as a Function of pH:** | not determined (see comments below) |
| **Adsorption/Desorption:** | not determined (see comments below) |
| **Dissociation Constant:** | no groups capable of dissociating are present (see comments below) |
| **Surface Tension:** | 70.9 mN/m at 20°C for a 90 % aqueous solution (see comments below) |
| **Flash Point:** | not determined (see comments below) |
| **Flammability Limits:** | not highly flammable, combustible |
| **Autoignition Temperature:** | > 400°C |
| **Explosive Properties:** | not determined; not expected to be explosive |
| **Reactivity/Stability:** | Expected to be stable under normal environmental conditions |

**Comments on Physico-Chemical Properties**

The Static technique was used for the determination of the vapour pressure at 20°C.

The column elution method, based on OECD Guideline 105, was used to determine the water solubility of the notified chemical. This method is suitable for solubilities below 0.10 g/L. However, the solubility value was very low and may be nearing the limit of detection for the method.

Hydrolysis, as a function of pH, could not be determined due to the low solubility of the notified chemical in water. The chemical contains ring lactones which would only hydrolyse under forcing conditions.

The partition coefficient was calculated from the structural formula of the test substance to be log $P_{ow}$ = 7.9 using the Rekker calculation method. Using the HPLC method, it was confirmed that log $P_{ow}$ > 6.2.

Adsorption/desorption testing was not performed. The notified chemical exhibits low water solubility and therefore entry into and through the soil profile is expected to be low. The notified chemical is expected to associate with the organic fraction of soil and sediments.

The dissociation constant could not be determined due to the low water solubility of the notified chemical. However, no groups are present which are likely to lose or gain a proton.

The notifier also provided a test report on surface tension of aqueous solutions of the notified chemical. The surface tension of a saturated water extract was diluted to produce a nominally 90% saturated solution. The surface tension of this solution was measured as 70.9 mN/m which shows that the material is not surface active. By definition, a chemical has surface activity when the surface tension is less than 60 mN/m (European Economic Community, 1992).

The flash point for the notified chemical was not determined as the chemical is a solid with a high melting point.

No experimental determinations of explosive properties or reactivity were performed, based on the absence of functional groups of high reactivity in the notified chemical.

## 4. PURITY OF THE CHEMICAL

Details of the purity of the notified chemical have been exempted from publication in the Full Public Report. The notified chemical contains no hazardous impurities at above the relevant cutoff concentrations for consideration of the impurities in determining the hazardous nature of the notified chemical.

## 5. USE, VOLUME AND FORMULATION

The notified chemical will be imported in the form of a powder containing a very high proportion of notified chemical.

The notified chemical will be used as a colourant in engineering plastics, including polyethylene terephthalate (PET), polybutylene terephthalate (PBT), polycarbonate (PC), polymethylmethacrylate (PMMA) and polystyrene (PS). The concentration in the final plastic article will typically be in the range 0.02 – 0.2 %.

The fastness properties are stated by the notifier to be excellent. The plastics containing the notified chemical are therefore likely to be used in applications such as traffic lights and automobile tail lights.

The notified chemical will be formulated initially to prepare masterbatches (colour concentrates in carrier resin, in pellet form); this may be further processed to produce

coloured plastic compound. Masterbatches or coloured compounds will be sold for further processing to produce the coloured plastic articles. Masterbatches will contain up to 10 % notified chemical, while coloured compounds will generally include the notified chemical at less than 0.2 %.

The notifier estimates that the import volume will be less than 1 tonne per year for the first five years of importation.

## 6. OCCUPATIONAL EXPOSURE

*Transport and Storage*
The notified chemical will be imported by both sea and air, in sealed cardboard boxes with antistatic plastic lining. The boxes will generally contain 10 to 20 kg notified chemical. Distribution will be by road. The notifier estimates that 5 to 10 workers will be involved in transport and storage of the notified chemical. These workers are not expected to be exposed to the notified chemical except in the case of an accident involving rupturing of the packaging.

*Laboratory*
Formulations will be established in laboratory trials, generally involving less than 100 g notified chemical. Formulation trials are expected to be infrequent, and to involve less than 1 hour exposure per trial. In addition, trials may be carried out on new batches of raw materials, involving less than 1 hour exposure every few months. Dermal and dust exposure are the most probable routes of exposure in these laboratory trials.

The notifier estimates that 10 to 25 laboratory staff could be exposed to the notified chemical. Protective clothing, impervious gloves, eye protection and respiratory protection are recommended by the notifier during these operations.

*Masterbatch Manufacture*
The notified chemical in powder form will be weighed using mechanical scales or load cells, and transferred by plant operators to the mixing area by forklift, trolley, or hand. The details of the weighing process have not been provided by the notifier, but it is likely to involve manual addition of the notified chemical to the weighing vessel. Exposure to the notified chemical in dust form is possible during weighing and transfer. The raw materials (polymer powder or granules, dyes and pigments, fillers and additives) are loaded into solid phase mixers/ blenders. The blenders are enclosed to avoid dust release. The pre-blend is then fed into the hopper of an extruder and then into the feed zone of the screws, where the blending is completed by melting the polymer. The action of the screws mixes the ingredients further. The melted polymer emerges from the extrusion head and is water cooled, pelletised, dried and packed into bags. The masterbatch produced in this process contains up to 10 % notified chemical. The approximate quantity of notified chemical per masterbatch formulation was not provided by the notifier.

From this point, the notified chemical will only be present in encapsulated form.

*Coloured Compound Manufacture*
Coloured compound may be directly formulated in a similar manner to masterbatch, or produced by blending masterbatch with additional resins. In the latter case, exposure to the

notified chemical is not expected, as it will be encapsulated in the polymer matrix of the masterbatch.

The notifier estimates that between 15 and 55 process workers, as well as 5 to 10 maintenance workers, will be involved in masterbatch and coloured compound manufacture. Exposure is estimated to be less than 4 hours per day, for 10 days per year at masterbatch manufacturers and 30 days per year at polymer compound manufacturing sites.

The weighing, blending and extrusion processes will occur under local exhaust ventilation. The workers in these processes are stated to wear gloves, safety glasses and overalls.

*Article Manufacture*
Process workers employed in the manufacture of finished articles are not expected to be exposed to the notified chemical as it will generally be used in the form of masterbatch or coloured compound, where the notified chemical will be encapsulated within the polymer matrix.

## 7. PUBLIC EXPOSURE

There is limited potential for exposure of the public to the notified chemical. Dust ventilated from formulation plants during masterbatch formulation is a potential source of public exposure. However, the amount of dust is expected to be small. Public exposure to the notified chemical after masterbatch formulation is considered to be unlikely since it is strongly bound in polymer matrices. Exposure to unbound chemical on plastic articles is likely to be negligible.

## 8. ENVIRONMENTAL EXPOSURE

### Release

The notified chemical will be reformulated at approximately 5-6 establishments in Australia. For ease of handling, plastic processors generally use colorants in the form of a masterbatch. The process usually consists of weighing and blending a thermoplastic polymer, dye and/or pigment powders and fillers, and additives. The ingredients are then melt-mixed, extruded, pelleted and packed.

*Masterbatch Formulation*
Less than 1 % of the notified chemical (as powdered dye) is expected to be spilled during weighing, blending and extrusion stages of the masterbatch formulating process. Dyestuff wastes will be released to sewer during cleaning of equipment and work areas. Presumably, solid, spilled, contaminated masterbatch granules will be swept up and disposed of to landfill. Whilst no details were provided regarding granule release via this avenue, this volume is expected to be low.

There is also potential for release to the atmosphere as dust, although this is expected to be low due to the relatively large particle size of the dye (99 % > 0.05 mm). Most of this waste will also be released to the sewer during cleaning of work areas and equipment.

The notifier estimates that less than 0.2 % of the dyestuff will be disposed of to landfill as residues in empty packaging.

*Plastic Processing*
The notifier states that most plastic sprue will be reprocessed into lower quality articles. Contaminated floor sweepings and over heated plastic scraps will be deposited into landfill. It is estimated that up to 5 % of the total annual import volume of the notified chemical could be released via this avenue.

Release may also occur as a result of spills during transport. The relatively small package sizes and particulate nature of the product, implies that spills would be minor and cleaned up easily.

Ultimately the majority of the notified chemical contained within plastic articles will be deposited to landfill or incinerated at the end of their useful life. According to the notifier, these plastics may also be recycled. However, recycling statistics were not provided, and the recycling level is likely to be very low at present.

**Fate**

*Fate of Dye in Powdered Form*
Release of the notified chemical into sewer is expected to occur at a rate of approximately 1 % per annum as a result of cleaning and minor dust emissions. This dye effluent will ultimately enter the aquatic compartment.

Ready Biodegradability of the notified chemical was tested (Desmares-Koopmans, 1998b) according to the modified Sturm test (OECD TG 301B). The theoretical $CO_2$ production of the notified chemical was calculated to be 2.88 mg $CO_2$/mg. The relative degradation values calculated from the measurements performed during the test period revealed no significant degradation of the notified chemical. In the toxicity control, the notified chemical was found to be not inhibitory. In conclusion, the notified chemical cannot be considered as readily biodegradable.

The notified chemical is poorly soluble in water (<4.52 μg/L), is not readily biodegradable (< 5 % in 30 days) and is not expected to hydrolyse in the environmental pH range. The log $P_{ow}$ value of > 6.2 suggests that the notified chemical will adsorb to aquatic sediment.

The notified chemical has the potential to bioaccumulate due to its relatively low molecular weight and log $P_{ow}$ > 6.2. However, bioaccumulation would be limited because of the low aquatic exposure, and the low water solubility is expected to limit absorption of the notified chemical through the gills.

Dye released into landfill as residues would be expected to adsorb to soil organic matter and remain relatively immobile. The notified chemical is expected to slowly degrade via biotic and abiotic processes.

*Fate of Dye in Polymer and Plastic Form*
In either the masterbatch or plastic form, the notified chemical will be firmly encapsulated by the polymer and is not expected to be mobile in landfill. In landfill, the notified polymer is

expected to slowly degrade as a result of biotic and abiotic processes. Incineration of products containing the notified chemical will produce water and oxides of carbon.

## 9. EVALUATION OF TOXICOLOGICAL DATA

Toxicological testing was performed using the pure notified chemical, referred to in the test reports as CG 33-0424.

### 9.1 Acute Toxicity

**Summary of the acute toxicity of ORACET Orange LGP**

| *Test* | *Species* | *Outcome* | *Reference* |
|---|---|---|---|
| acute oral toxicity | rat | $LD_{50}$>2000 mg/kg | (Pels Rijcken, 1998c) |
| acute dermal toxicity | rat | $LD_{50}$>2000 mg/kg | (Pels Rijcken, 1998b) |
| skin irritation | rabbit | non-irritating | (Pels Rijcken, 1998e) |
| eye irritation | rabbit | slight irritant | (Pels Rijcken, 1998a) |
| skin sensitisation | guinea pig | sensitising | (Pels Rijcken, 1998d) |

#### 9.1.1 Oral Toxicity (Pels Rijcken, 1998c)

| | |
|---|---|
| *Species/strain:* | rat/Wistar |
| *Number/sex of animals:* | 3/sex |
| *Observation period:* | 15 days |
| *Method of administration:* | gavage at 2000 mg/kg in olive oil, as a 10 mL/kg dose |
| *Test method:* | OECD TG 423 |
| *Mortality:* | no mortality occurred |
| *Clinical observations:* | no clinical signs of toxicity were observed |
| *Morphological findings:* | no abnormalities were found at macroscopic post mortem examination |
| *Comment:* | red staining of the faeces by the test substance was observed in all animals on day 1 and/or day 2 and in addition red staining of the tail was observed in one animal between days 1 and 6<br><br>no adverse effect was noted on body weight gain of treated animals compared with controls |

| | |
|---|---|
| *$LD_{50}$:* | >2000 mg/kg |
| *Result:* | the notified chemical was of very low acute oral toxicity in rats |

### 9.1.2 Dermal Toxicity (Pels Rijcken, 1998b)

| | |
|---|---|
| *Species/strain:* | rat/Wistar |
| *Number/sex of animals:* | 5/sex |
| *Observation period:* | 15 days |
| *Method of administration:* | a single, 24 hour, semi-occluded topical application to intact skin; dose level 2000 mg/kg in olive oil (10 mL/kg) |
| *Test method:* | OECD TG 402 |
| *Mortality:* | no mortality occurred |
| *Clinical observations:* | on day 2, lethargy and/or tremors were noted in two males and red staining of the head was noted in one female<br><br>scales were seen in the treated skin-area of two animals between days 6 and 9; orange staining of the back and/or abdomen by the test substance was observed in all animals during the observation period |
| *Morphological findings:* | no abnormalities were found at macroscopic post mortem examination<br><br>watery fluid in the uterus of one female was considered to be related to a stage in the oestrous cycle and therefore normal |
| *Comment:* | Considerable body weight loss was observed in one male over the observation period; no cause could be attributed except that the animal suffered lethargy and tremors on day 2 only<br><br>although other males in the group had normal weight gain, the possibility of a treatment-related effect could not be excluded<br><br>two females showed a slight body weight loss during the second week post treatment<br><br>on the basis of an established acute oral LD50 of >2000 mg/kg, it seems unlikely that the sporadic weight loss in the few test animals is treatment-related |

| | |
|---|---|
| *$LD_{50}$:* | >2000 mg/kg |
| *Result:* | the notified chemical was of low dermal toxicity in rats |

### 9.1.3 Inhalation Toxicity

The notifier stated that an inhalation toxicity test was not conducted. It was stated that inhalation was not considered to be major route of exposure, as 99.8% of the notified chemical has a particle size > 20µm.

### 9.1.4 Skin Irritation (Pels Rijcken, 1998e)

| | |
|---|---|
| *Species/strain:* | rabbit/New Zealand White |
| *Number/sex of animals:* | 3 males |
| *Observation period:* | 3 days |
| *Method of administration:* | a single 4 hour semi-occluded application of 0.5 gm of test substance to intact skin |
| *Test method:* | OECD TG 404 |
| *Comment:* | scoring for erythema one hour after exposure was not possible because of skin staining; a red/orange staining of the treated skin by the test substance was evident throughout the observation period<br><br>there was no evidence of a corrosive effect on the skin; no symptoms of systemic toxicity were observed in the animals during the test period and no mortality occurred |
| *Result:* | the notified chemical was considered non-irritating to the skin of rabbits |

### 9.1.5 Eye Irritation (Pels Rijcken, 1998a)

| | |
|---|---|
| *Species/strain:* | rabbit/New Zealand White |
| *Number/sex of animals:* | 3 males |
| *Observation period:* | 3 days |
| *Method of administration:* | approximately 55 mg of the test substance, in 0.1 mL solution, was instilled in the conjunctival sac of one eye of each animal; the lid was gently held together for about a second to prevent loss of test substance |

| | |
|---|---|
| *Test method:* | OECD TG 405 |
| *Comment:* | one hour after instillation of the test substance, there was irritation of the conjunctiva, which consisted of redness, chemosis and discharge; the irritation completely resolved within 24 hours in all animals<br><br>mean values for eye irritation scores (24 to 72 hours post instillation) were zero |
| *Result:* | the notified chemical was slightly irritating to the eyes of rabbits |

### 9.1.6 Skin Sensitisation (Pels Rijcken, 1998d)

| | |
|---|---|
| *Species/strain:* | guinea pig/Dunkin Hartley albino |
| *Number of animals:* | test group: 10 females<br>control group: 5 females |
| *Induction procedure:* | day 1:<br>three pairs of intradermal injections (0.1 mL) were made to the scapular region<br>- 1:1 w/w mixture of Freund's Complete Adjuvant (FCA) with water;<br>- 2 % concentration of test substance in olive oil;<br>- 1:1 w/w mixture of 4 % test substance and FCA<br><br>day 3:<br>dermal reactions caused by the intradermal injections were assessed for irritation<br><br>day 7:<br>10 % SDS was applied to the scapular area between the injection sites<br><br>day 8:<br>the 10 % SDS-treated area was treated with 0.5 mL of a 50 % test substance concentration applied as a patch; after 48 hours, residual test substance was cleaned off and dermal reactions were scored |
| *Challenge procedure:* | day 22:<br>0.5 mL of 50 % test substance in olive oil and 0.5 mL olive oil were applied to the epidermis of the flank by patches<br><br>the dressing was removed after 24 hours and the challenge reactions were assessed after a further 24 and 48 hours |

*Test method:* OECD TG 406; Maximisation Test of Magnusson and Kligman

*Challenge outcome:*

| ***Challenge concentration*** | ***Response Grade*** | ***Test animals*** | | ***Control animals*** | |
|---|---|---|---|---|---|
| | | ***24 hours**** | ***48 hours**** | ***24 hours*** | ***48 hours*** |
| vehicle | 1 | **5/10 | 7/10 | 0/5 | 0/5 |
| | 2 | 0/10 | 1/10 | 0/5 | 0/5 |
| | 3 | 0/10 | 0/10 | 0/5 | 0/5 |
| | scaliness | 0/10 | 5/10 | 0/5 | 2/5 |
| 50% | 1 | 5/10 | 4/10 | 0/5 | 0/5 |
| | 2 | 3/10 | 4/10 | 0/5 | 0/5 |
| | 3 | 0/10 | 1/10 | 0/5 | 0/5 |
| | scaliness | 0/10 | 7/10 | 0/5 | 1/5 |

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

*Comment:* Positive skin reactions were observed in nine experimental animals in response to the 50% test substance concentration. No positive skin reactions were evident in the control animals. Scaliness was seen in treated skin sites among the experimental and control animals at the 48 hour observation.

In eight of the test animals, a positive response was also observed in the vehicle-treated skin site. In all cases, the animal showed an equal or greater response at the test substance treated site. The testing laboratory claimed that since the control animals also received vehicle treatment in the induction phase, sensitisation to the vehicle was ruled out, based on the absence of positive responses in the control group to the vehicle.

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

## 9.2 Repeated Dose Toxicity (Pels Rijcken, 1998f)

*Species/strain:* rat/Wistar

*Number/sex of animals:* 6 groups, 5/sex/group

*Method of administration:* oral gavage in vehicle (olive oil)

*Dose/Study duration:*

| Group ID | dose level (mg/kg/day) |
|---|---|
| control | vehicle |
| control recovery | vehicle |
| test (low dose) | 50 |
| test (medium dose) | 200 |
| test (high dose) | 1000 |
| test (high dose) recovery | 1000 |

dose volume was 5 mL/kg body weight, adjusted weekly

animals were treated once daily, for 28 consecutive days

recovery groups were kept for a further 14 days, without treatment

*Test method:* OECD TG 407

*Clinical observations:*

No treatment-related mortality occurred during the study period. One female of the 1000 mg/kg/day group died accidentally during blood sampling at the end of the recovery period.

There were no treatment-related clinical signs of systemic toxicity or behavioural changes over the observation period. Red discolouration of faeces of the 1000 mg/kg/day animals was apparent from day 2 of the treatment onwards, disappearing after cessation of treatment.

Females only, in the 1000 mg/kg/day group, had slightly lower overall motor activity. This finding was stated to be of minimal severity.

Body weights and body weight gain of treated animals remained in the same range as controls over the 4-week treatment period. During the recovery period, the body weight gain of the high-dose females was lower compared with controls.

*Clinical chemistry/Haematology*

No treatment-related haematological effects were considered by the study authors to have occurred. No importance was placed on the finding that females in the 1000 mg/kg/day group had a statistically significant decrease in WBC after the 2-week recovery period.

After 4 weeks, inorganic phosphate levels in both sexes of the 200 and 1000 mg/kg/day groups were significantly lower than controls, but the values were within the historical background range. A decrease in ALT and AST noted in some treated animals was also considered to have no biological relevance.

*Histopathology:*

No treatment-related macroscopic findings were seen after the 4-week treatment period.

Dark red discolouration of the renal medulla was found in two high dose males at necropsy after the recovery period. No further abnormalities were found in animals of the recovery groups.

After the 4-week treatment period, organ weights and organ/body weight ratios of treated animals were in the same range as controls.

As a consequence of the difference in terminal body weights between controls and high dose females after the recovery period, the weights for heart and thymus, and the brain/body weight ratio achieved levels of statistical significance.

There were no treatment-related microscopic findings noted in organs and tissues examined from controls and high dose animals at the end of the 4-week treatment.

*Comment:*

Very little toxicological relevance could be attributed to any of the statistically significant variations in parameters noted between treated and controls groups. Differences in motor activities for the females were slight and not replicated in the males or in the lower dose groups.

*Result:*

The notified chemical was considered to have a No Observed Adverse Effect Level (NOAEL) of 1000 mg/kg/day

## 9.3 Genotoxicity

### 9.3.1 *Salmonella typhimurium* and *Escherichia Coli* Reverse Mutation Assay (Verspeek-Rip, 1998)

| | |
|---|---|
| *Strains:* | *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100<br>*Escherichia coli* WP2 uvrA |
| *Concentration range:* | Experiment 1<br>0, 10, 33, 100, 333, 1000, 3333 and 5000 μg/plate<br><br>experiment 2:<br>0, 1, 3, 10, 33 and 100 μg/plate |
| *Metabolic activation:* | 5 % and 10 % rat liver S9 fraction (Aroclor 1254) with standard cofactors in experiments 1 and 2, respectively |
| *Positive controls:* | without S9:<br>TA1535, sodium azide, 1 μg/plate<br>TA1537, 9-aminoacridine, 60 μg/plate<br>TA98, daunomycin, 4 μg/plate<br>TA100, methylmethanesulfonate, 650 μg/plate |

| | |
|---|---|
| | WP2uvrA, 4-nitroquinoline N-oxide, 10 μg/plate<br><br>with S9:<br>TA1537, 2-aminoanthracene, 2.5 μg/plate<br>TA1535, TA98, and TA100, 2-aminoanthracene, 1 μg/plate<br>WP2uvrA, 2-aminoanthracene, 5 μg/plate |
| *Test method:* | OECD TG 471 and TG 472, plate incorporation method |
| *Comment:* | In both experiments, the test substance precipitated in the top agar at concentrations of 33 μg/plate and upwards, but did not interfere with the integrity of the study.<br><br>No reduction in the bacterial background lawn and no decrease in the number of revertants was observed.<br><br>No significant increases in mutant frequency were noted for any of the tester strains, in the presence and absence of S9. All positive controls responded appropriately |
| *Result:* | the notified chemical was considered to be non-mutagenic under the conditions of the assay |

**9.3.2 Chromosomal Aberration Assay in Human Peripheral Lymphocytes (Bertens, 1998)**

| | |
|---|---|
| *Cells:* | human peripheral lymphocytes |
| *Metabolic activation system:* | 1.8% v/v liver S9 fraction (Aroclor 1254) with standard cofactors |
| *Dosing schedule:* | <u>Experiment 1:</u><br>without S9<br>0, 1, 3, 10 and 33 μg; 3 h treatment, 24 h fixation;<br>0, 1, 3, 10 and 33 μg; 24 h treatment, 24 h fixation;<br>0, 1, 3, 10 and 33 μg; 48 h treatment, 48 h fixation;<br><br>with S9<br>1, 3, 10 and 33 μg; 3 h treatment, 24 h fixation;<br>1, 3, 10 and 33 μg; 48 h treatment, 48 h fixation.<br><br><u>Experiment 2</u><br>without S9<br>0, 1, 3, 10 and 33 μg; 24 h treatment, 24 h fixation;<br><br>withS9<br>0, 1, 3, 10 and 33 μg; 3 h treatment, 24 h fixation. |

| | |
|---|---|
| | the test substance was dissolved in DMSO; all cultures were in duplicate |
| *Positive controls:* | without S9:<br>mitomycin C at 0.5 μg/mL for 3 h treatment;<br>0.2 μg/mL for 24 h treatment; and<br>0.1 μg/mL for 48 h treatment<br><br>with S9:<br>cyclophosphamide at 15 μg/mL for 3 h treatment |
| *Test method:* | OECD TG473 |
| *Comment:* | The test substance did not induce a statistically or biologically significant increase in the number of cells with chromosomal aberrations in the presence and absence of S9, in the two independently repeated experiments.<br><br>All positive controls responded appropriately |
| *Results:* | the notified chemical was considered to be non-clastogenic under the conditions of the assay |

### 9.3.3 Micronucleus Assay in the Bone Marrow Cells of the Mouse

The notifier stated that this test was not performed, as it was not required for EEC notification and as both *in vitro* tests gave negative results.

## 9.4 Overall Assessment of Toxicological Data

A toxicokinetic assessment of the notified chemical was provided by the notifier (Groen, 1998). It was concluded that the notified chemical may penetrate skin, and has potential for accumulation in fatty tissues, due to the high value for $K_{ow}$. It is not expected to be readily absorbed from the gastro-intestinal tract due to the low water solubility. The structure indicates that ready hydroxylation and conjugation followed by excretion in the body is expected.

The notified chemical, ORACET Orange LGP, has very low oral toxicity in the rat, with an $LD_{50}$ > 2000 mg/kg.

In a dermal toxicity study, there was considerable body weight loss in one male over the observation period but no cause could be attributed except that the animal suffered lethargy and tremors on day 2 only. Although other males in the group had normal weight gain, the possibility of a treatment-related effect could not be excluded. Two females showed a slight body weight loss during the second week post treatment. On the basis of an established acute oral $LD_{50}$ of > 2000 mg/kg, it seems unlikely that the sporadic weight loss in the few test animals is treatment-related. Therefore it was considered that the notified chemical has an $LD_{50}$ > 2000 mg/kg in the dermal toxicity study.

An inhalation toxicity test was not conducted. A small proportion (between 5.5 % and 18.8 %) of the chemical is within the inspirable size range, however no conclusion on the inhalation toxicity can be reached. As the notified chemical exists in powder form and is an experimental skin sensitiser, the possibility of respiratory sensitisation cannot be excluded.

The notified chemical is not a skin irritant. In an eye irritation study, however, there was irritation of the conjunctiva one hour after application, which consisted of redness, chemosis and discharge. Within 24 hours, all symptoms resolved.

In a maximisation skin sensitisation study, positive skin reactions were observed in nine experimental animals in response to the 50% test substance concentration. No positive skin reactions were evident in the control animals. Scaliness was seen in some treated skin sites among the experimental and control animals, 48 hours after the challenge exposure only. In eight of the experimental animals, a positive response was also observed in the vehicle-treated skin site. The testing laboratory claimed that since the control animals received vehicle treatment in the induction phase, sensitisation to the vehicle was ruled out, based on the absence of positive responses in the control group to the vehicle.

A repeat dose toxicity study revealed some statistically significant differences between treated and control animals, including some haematological parameters, but none were considered to be treatment-related. A NOAEL of 1000 mg/kg/day was established in this study.

ORACET Orange LGP did not induce mutations in *S typhimurium* or *E. coli* reversion assays and was non-clastogenic in human peripheral lymphocytes.

*Hazard classification*
According to the skin sensitisation data, ORACET Orange LGP meets the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999a) criteria to be classified as a Sensitiser (Xi) and will require the risk phrase R43, "May cause sensitisation by skin contact" to be assigned.

## 10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

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

| ***Species*** | ***Test*** | ***Concentrations[a] (mg/L)*** | ***Result(mg/L)*** |
|---|---|---|---|
| Carp *(Cyprinus carpio)* | 96 h acute | 100 | $LC_{50} > 100$ |
| Water Flea (*Daphnia magna*) | 48 h acute | 100 | $EC_{50} > 100$ |
| Algae (*Selenastrum capricornutum* ) | 96 h growth | 100 | $E_RC_{50} > 100$<br>$E_BC_{50} > 100$ |
| Activated Sludge | 30 min | 100 | $LC_{50} > 100$ |

[a]test concentrations are nominal only.

The notified chemical has low water solubility (4.5 μg/L). In response to this, for each toxicity test undertaken, two solutions were prepared at nominal concentrations of 100 mg/L. Measured concentrations declined during the test period due to precipitation and settling of undissolved test substance particles. Duplicate supersaturated solutions were stirred for 66 hours. One of these solutions was filtered twice through paper filter (5.0 μm) to remove undissolved test substance particles. The filtered solution was a clear pink color. The other test solution remained unfiltered and remained a turbid red color. Solutions were produced for each toxicity test and were used to ascertain toxicity levels for carp, daphnia, algae and waste water bacteria.

Fish toxicity testing (Bogers, 1998a) was carried out according to OECD TG 203. Test solutions were prepared as outlined above. $LC_{50}$ values could not be determined because no mortalities were observed during the 96 hour experiment. Under the test conditions, exposure to the supersaturated solutions of the notified chemical induced no acute effects in carp. The highest measured concentration at the end of the test period was 10 mg/L, which greatly exceeded the water solubility of < 0.0045 mg/L.

The acute toxicity study of *Daphnia magna* with the notified chemical (Bogers, 1998b) was based on OECD TG 202. Due to the low solubility of the notified chemical in water, testing solutions were prepared as outlined above. Exposure to the supersaturated solutions of the notified chemical induced no acute effects in daphnia. The highest measured concentration at the end of the test period was 2.7 mg/L, which greatly exceeded the water solubility of < 0.0045 mg/L.

The fresh water algal growth inhibition test with the notified chemical (Bogers, 1998c) was based on OECD TG 201. Exposure to the supersaturated solutions of the notified chemical induced no acute effects in the alga *Selenastrum capricornutum* at loadings largely exceeding the level of water solubility. The highest measured concentration at the end of the test period was 0.79 mg/L, which greatly exceeded the water solubility of < 0.0045 mg/L.

The influence of the notified chemical on the respiration rate of activated sludge was investigated (Desmares-Koopmans, 1998a) according to OECD TG 209. These guidelines indicate that a figure of 10% inhibition is considered to be significant. Based on this criterion, no significant inhibition in respiration rate of the sludge was recorded at approximately 100 mg/L. The respiration rates of the controls were within 15% of each other. The $EC_{50}$ of the reference substance (3,5-dichlorophenol) was 9 mg/L.

The ecotoxicity data indicate that, based on the conditions of individual tests, the notified chemical is not toxic to carp, daphnia, algae and waste water bacteria to the limit of its water solubility.

## 11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The majority of the notified chemical will ultimately be released to landfill or incinerated either as masterbatch waste, as sprue or plastic products at the end of their useful life. The notified chemical is poorly water soluble, and when bound within a polymer matrix, either as a masterbatch or as plastic articles, little release is expected to occur. Except in the case of accidental release during transport, the primary source of release of the colourant will be associated with the slow degradation of plastic and masterbatch granules into which the

dyestuff is incorporated. This release will be diffuse, and is unlikely to lead to toxic concentrations of the chemical.

Only a small percentage (1 %) of the notified chemical as a dyestuff is expected to enter the aquatic compartment per year as a result of weighing, blending and during cleaning of equipment and work areas. Ecotoxicity data indicate that the notified chemical, to the limit of its solubility, is not toxic to carp, daphnia, algae and waste water bacteria.

The low volume of the notified chemical entering the aquatic compartment coupled with the low solubility and low apparent toxicity to aquatic organisms indicate that the risks associated with the use of the notified chemical are low.

When used as indicated in the notification, the new chemical is unlikely to present a hazard to the environment.

## 12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The acute toxicity of ORACET Orange LGP is low, and it is not an irritant to the skin of rabbits. It is a slight irritant to rabbit eyes. The notified chemical was found to be a skin sensitiser in an adjuvant type skin sensitisation study in guinea pigs.

For longer-term systemic effects, the NOAEL is 1000 mg/kg/day, as no toxicologically relevant changes were observed at any dose used in a 28 day oral rat study. The notified chemical was not found to be genotoxic in an *in vitro* bacterial point mutation assay and a human peripheral lymphocyte chromosomal aberration assay.

The notified chemical may present a major hazard by inhalation, with between 5.5 % and 18.8 % of the particles within the inspirable range. As the notified chemical is a skin sensitiser, it is possible that it is also a respiratory sensitiser, and precautions to minimise inhalation exposure should accordingly be taken. An exposure limit of 0.1 mg/m$^3$ (TWA) should be applied to the notified chemical in line with UK chemical industry recommendations for powdered colourants which are known skin sensitisers (Chemical Industries Association Dyes Sector Group, 1992).

*Occupational Health and Safety*
Occupational exposure to the notified chemical can be divided into exposure to the powdered solid and to coloured plastic in masterbatch or coloured compound form. The notified chemical is expected to be encapsulated in the resin in the latter case, and not be separately available for exposure. The powdered solid will be a potential hazard by dermal and ocular exposure. A small proportion will also be available for inhalation exposure.

*Transport and Storage*
The health risk for transport and storage workers is expected to be negligible unless the packaging is breached.

*Masterbatch Preparation*
The notified chemical will generally be initially formulated with polymer powder or granules and other additives to produce a masterbatch, which will then be further blended, possibly at

other sites, to produce the final coloured articles. Workers involved in preparing masterbatches may be exposed to the powdered solid, either by skin contact or inhalation exposure to atmospheric dust. The notifier states that blending will occur in an enclosed system to reduce dust exposure. There is a risk of respiratory sensitisation from handling the powder, as it has been shown to be a skin sensitiser and no information has been provided to indicate that it is not a respiratory sensitiser. Also a significant fraction of the powder is in the inspirable size range. There is also a risk of skin sensitisation during handling of the powder, but this will be minimised by the use of personal protective equipment (PPE).

*Masterbatch Use*
Little exposure to the notified chemical is expected for workers handling masterbatches or pre-prepared coloured polymer compound in the production of articles. The notified chemical will be encapsulated in the polymer matrix and will not be available for separate exposure, and therefore the risk of adverse health effects arising from the use of the notified chemical is negligible.

*Laboratory*
Laboratory workers will be exposed to small quantities of the notified chemical for short periods. Local exhaust ventilation and personal protective equipment, including respiratory protection, should be available as required. However, there is some risk of respiratory and skin sensitising effects from handling the notified chemical.

*Public Health*
There is negligible potential for public exposure to the notified chemical arising from its use as a dyestuff in plastic articles. Based on the toxicity profile and use pattern of the notified chemical, it is considered that the notified chemical will not pose a significant hazard to public health.

## 13. RECOMMENDATIONS

To minimise occupational exposure to ORACET Orange LGP the following guidelines and precautions should be observed:

- The notified chemical may be recommended to the National Occupational Health and Safety Commission for consideration for inclusion in the NOHSC List of Designated Hazardous Substances;
- An exposure limit of 0.1 mg/m$^3$ (TWA)for the notified chemical should be observed in the workplace;
- Where engineering controls are insufficient to reduce the atmospheric concentration of dust to the recommended limit, respiratory protection according to Australian Standard (AS) 1716 (Standards Australia/Standards New Zealand, 1994a) should be used while handling the powdered dyestuffs;
- Individuals who become sensitised should not continue to handle the notified chemical;

- Safety goggles should be selected and fitted in accordance with Australian Standard (AS) 1336 (Standards Australia, 1994) to comply with Australian/New Zealand Standard (AS/NZS) 1337 (Standards Australia/Standards New Zealand, 1992); industrial clothing should conform to the specifications detailed in AS 2919 (Standards Australia, 1987) and AS 3765.2 (Standards Australia, 1990); impermeable gloves should conform to AS/NZS 2161.2 (Standards Australia/Standards New Zealand, 1998); all occupational footwear should conform to AS/NZS 2210 (Standards Australia/Standards New Zealand, 1994b);

- Spillage of the notified chemical should be avoided. Spillages should be swept up promptly and 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.

If the conditions of use are varied from the notified use, greater exposure of the public may occur. In such circumstances, secondary notification may be required to assess the hazards to public health.

## 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, secondary notification of the notified chemical may be required if any of the circumstances stipulated under Section 64 of the Act arise. No other specific conditions are prescribed.

## 16. REFERENCES

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## Attachment 1

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

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

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

***CORNEA***

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

***CONJUNCTIVAE***

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

***IRIS***

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