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August 2007

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Florhydral

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 Water Resources.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full Public Report is also 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:

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Givaudan Pty Ltd (ABN 87 000 470 280)
9 Carolyn St
Silverwater NSW 2128

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
The chemical has been previously notified to NICNAS under LVC/555.

NOTIFICATION IN OTHER COUNTRIES
EU, Level 1A (10-100T) from 2005
CANADA: max. 1000kg/year, 1999;
USA/TSCA: PMN without weight limitation, 1989

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
Benzenepropanal, β-methyl-3-(1-methylethyl)-

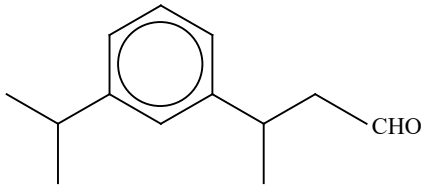
OTHER NAME(S)
3-(3-isopropylphenyl)butanal
Butanal, 3-[3-(1-methylethyl)phenyl]-
GR-82-4130

MARKETING NAME(S)
Florhydral

CAS NUMBER
125109-85-5

MOLECULAR FORMULA
$C_{13}H_{18}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT

190.3 g/mol

ANALYTICAL DATA
Reference NMR, IR, GC, GC-MS, and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
99.3%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)
None

ADDITIVES/ADJUVANTS

Chemical Name	Alpha Tocopherol (2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-)		
CAS No.	10191-41-0	*Weight (ppm)*	200
Chemical Name	Citric Acid (2-Hydroxy-1,2-propanetricarboxylic acid)		
CAS No.	77-92-9	*Weight (ppm)*	40

4. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Colourless to pale yellow liquid

Property	Value	Data Source/Justification
Freezing Point	<-50ºC	Measured
Boiling Point	257ºC at 101.3 kPa	Estimated from vapour pressure curve
Density	953 kg/m^3 at 20ºC	Measured
Vapour Pressure	0.001-0.003 kPa at 20ºC	Measured
Water Solubility	0.04 g/L at 20ºC	Measured
Fat Solubility	Miscible in all proportions with the standard fat sample	Measured
Hydrolysis as a Function of pH	$t_{1/2}$ = 710 h (pH 4); 620 h (pH 7); 2000 h (pH 9)	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.8	Measured
Surface Tension	52.4 mN/m at 20°C	Measured
Adsorption/Desorption	log K_{oc} = 3.18	Estimated
Dissociation Constant	Not determined	The notified chemical is not expected to dissociate as it contains no dissociable groups
Flash Point	68ºC at 101.3 kPa	Measured
Flammability	Not spontaneously flammable. Does not emit flammable gases in contact with water or moist air. Note expected to form flammable mixtures in air.	Statement by notifier
Autoignition Temperature	245ºC	Measured
Explosive Properties	Not expected to be explosive	Estimated based on chemical structure
Oxidising Properties	Not expected to be oxidising	Estimated based on chemical structure

Discussion of Observed Effects

For full details of the physical-chemical properties tests please refer to Appendix A.

Reactivity
The notified chemical is expected to be stable in water and air under normal conditions of temperature and pressure. The notifier states that rags impregnated with similar fragrance materials (particularly aldehydes and terpenes) left unattended in a dustbin have caught fire. In light of these two facts, precautions should be taken to prevent combustion. The notifier states flushing rags impregnated with fragrance materials with water should prevent this risk.

Dangerous Goods classification
Based on the flash point the notified chemical would be classified as a C1 combustible liquid. The notified chemical has been classified by the notifier as a Dangerous Good Class 9, Packing Group III, UN Number 3082 Environmentally Hazardous Substance, Liquid, N.O.S., according to the Australian Dangerous Goods Code (FORS, 1998).

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a component of fragrance compounds (< 5%).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.10	0.12	0.14	0.16	0.18

PORT OF ENTRY
Sydney (by sea or air)
Perth (by air)

IDENTITY OF MANUFACTURER/RECIPIENTS
Givaudan Pty Ltd

TRANSPORTATION AND PACKAGING
The fragrance blends containing up to 5% of the notified chemical are imported in glass, lacquer-lined containers. The proposed standard packaging sizes are: 1, 5, 10, 25, 100 and 190 kg. The blends will be transported by road in sealed containers to formulators. The finished product containing up to 1% of the notified chemical will be transported to industrial customers or retail outlets.

USE
The notified chemical will be used as an aroma chemical in alcoholic perfumery, cosmetics, toiletries, household products, soaps, detergents and industrial perfumery. The concentration of the notified chemical in fragrance compound is up to 5%. The concentration of the notified chemical in end-use consumer products will be up to 1% in alcohol-based perfumes, and typically 0.15% in soaps and 0.05% in detergents.

OPERATION DESCRIPTION
Details on how the notified chemical is to be used are not available to the notifier. The following is a typical operation description for similar chemicals in fragrance compounds.

The notified chemical will be imported as a component of a liquid fragrance mixture at up to 5%.

Formulation
If imported as a component of a liquid fragrance mixture, the mixture will be blended with other ingredients at customer formulation sites, to make end-use consumer products, such as alcoholic perfumes, cosmetics, toiletries, household products, detergents and soaps. While the formulation process will vary with the product type and formulation site, it is expected that most sites will have closed, automated mixing and dosing equipment. The packaged consumer products will be transported to retail outlets for sale to the public.

End use
There is potential for the formulated products to be used occupationally, for example by professional cleaners using cleaning products (containing 0.05%) or beauticians using cosmetic products (containing up to 1%).

Cleaning products are generally applied with a cloth or sponge, by mop or brush or by spray followed by wiping. In some cases, the cleaning product will be diluted with water prior to application. The dilution factor, which is often on the label, depends on the type of surface to be cleaned, the soil loading, and the type and method of application.

Depending on the nature of the cosmetic product these could be applied a number of ways such as by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure assessment

6.1.1. Occupational exposure

Number and Category of Workers
Details of occupational exposure are not available to the notifier. The following occupational exposure table is given as an example of the likely exposure based on similar chemicals in fragrance compounds.

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and Warehouse workers	5	None	Incidental Exposure only
Plant operators			
Mixer	5	4 hr/day	2 days/year
Drum handling	5	4 hr/day	2 days/year
Drum cleaning/washing	10	4 hr/day	2 days/year
Maintenance	5	4 hr/day	2 days/year
Quality control worker	2	0.5 hr/day	2 days/year
Packager	10	4 hr/day	2 days/year
End users (professionals)	> 1000	1-8	200 days/year

Exposure Details
Details on customer blending operations, worker exposure and life cycle of the notified chemical are not available to the notifier. The number and category of workers will vary depending on the nature of the customers' business. However, it is anticipated that typical practices by cosmetic and consumer product manufacturers will include the use of adequate local ventilation, appropriate PPE, enclosed mixing vessel and filling areas as well as a high degree of process automation to protect workers.

At the customer facilities, transport and warehouse workers will be exposed to the fragrance mixture (up to 5% notified chemical) only in the event of a spill due to an accident or leaking drum. Workers will wear protective overalls, hard hats, chemical resistant gloves and safety glasses.

At customer facilities (cosmetic and consumer product manufacturers), exposure to the fragrance mixture (up to 5% notified chemical) or products containing the notified chemical (0.05-1%) is possible during handling of the drums, cleaning and maintenance of the equipment. Skin, inhalation and eye contact (due to splashing) are likely to be the main routes of exposure. The level of exposure would vary from site to site depending on the level of automation of the formulation process. The worst case dermal exposure is expected to be to workers directly handling the imported fragrance mixture, and is estimated to be 0.005-0.05 mg/cm^2/day, based on EASE model (EASE) using reasonable worst case defaults for the exposure scenario 'manual addition of liquids' (European Commission, 2003) and assuming the notified chemical is present at concentration of 5%. Therefore, assuming a surface area of 420 cm^2 (one hand) for a 70 kg worker and a 100% dermal absorption factor, systemic exposure is estimated to be 0.03-0.3 mg/kg bw/day. Exposure is likely to be minimised

by good personal hygiene practices (eg. washing hands after any contact, before breaks and meals, etc) and use of industrial standard PPE.

According to EASE (1997) modelling of this work environment, in which it is assumed that non-dispersive use occurs in the presence of local exhaust ventilation, the estimated atmospheric concentration during handling of the imported fragrance oil (5% notified chemical) is 0.025-0.05 ppm (0.19-0.39 mg/m^3). Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/h, and 4 hour exposure, systemic exposure after inhalation is estimated to be 0.014-0.029 mg/kg bw/day. This estimate assumes that no respiratory protection is worn.

The worst-case total systemic exposure from the dermal and inhalation routes is therefore estimated as 0.044-0.33 mg/kg bw/day.

End use
Exposure to no more than 1% notified chemical could occur during final application of the cleaning/cosmetic products or during their addition to water if dilution is required. The main route of exposure is expected to be dermal, although ocular exposure to splashes is possible and inhalation of aerosols could occur where application is by spray. Although the level and route of exposure will vary depending on the method of application and work practices employed, exposure is considered to be low due to the low concentration of the notified chemical.

6.1.2. Public exposure

End-use products are designed to be sold to consumers. The general public will be repeatedly exposed to low-levels of the notified chemical via a number of different consumer products (typical levels 0.01-1%).

Acute dermal exposure
Use of perfumery products (such as toilet waters) are expected to give the highest single exposure because of the relatively high concentration of the products applied to the skin, and the "leave-on" nature of these products. The maximum dermal exposure is estimated as shown below using consumer exposure data from two different sources. In all calculations the retention factor for these products is assumed to be 1.

	Perfumery products	
Data Source	Cadby/SCCP[a]	Tozer[b]
Quantity product applied (mg)	750	-
Surface Area (cm^2)	100	-
Exposure to product (μg/cm^2)	7500	2210
Concentration of notified chemical (%)	1.0	1.0
Exposure to notified chemical (μg/cm^2)	75	22.1

[a] Amount per application taken from data presented in Cadby et al. (2002); surface area taken from data given in SCCP's Notes of Guidance (SCCP, 2006)
[b] Measured and modelled data presented in Tozer et al. (2004)

Chronic dermal exposure
The worst-case long-term dermal exposure to the notified chemical can be estimated by assuming that the notified chemical is present in the maximum amount in all cosmetic products used by the consumer, and that there is 100% dermal absorption. The estimated skin surface residue to fragrances due to use of a number of cosmetic products is estimated as 2.547 mg/kg bw/day (from Cadby, 2002). Therefore based on a concentration of 5% notified chemical in the fragrance compound the long-term dermal exposure to the notified chemical is estimated as 0.127 mg/kg bw/day.

Public exposure from transport, storage, reformulation or disposal is considered to be negligible.

Since products containing the notified chemical are stored and used in a domestic environment, there is the possibility of accidental ingestion by a child.

6.2. Human health effects assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	Low toxicity, LD50 > 2000 mg/kg bw
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test.	no evidence of sensitisation
Guinea pig, skin sensitisation –non-adjuvant test.	limited evidence of sensitisation
Human, skin sensitisation – Repeat Insult Patch Test	no evidence of sensitisation at 5% concentration
Rat, repeat dose oral (gavage) toxicity – 28 days.	NOEL = 60 mg/kg bw/day
Phototoxicity	no phototoxic potential
Genotoxicity – bacterial reverse mutation (*S. Typhimurium*)	non mutagenic
Genotoxicity – bacterial reverse mutation (*E. Coli*)	non mutagenic
Genotoxicity – in vitro chromosome aberration test (Chinese Hamster V79 cells)	non genotoxic
Genotoxicity – in vivo mouse micronucleus test	non genotoxic

Acute toxicity
Based on the test in rats the notified chemical exhibits low acute toxicity via oral exposure.

Irritation Sensitisation
The notified chemical was slightly irritating to skin when tested undiluted on rabbits, producing slight erythema in all animals 24 hours after exposure. All reactions had resolved by 72 hours. The notified chemical is slightly irritating to eyes when tested in rabbits, producing only slight conjunctival redness and swelling after 1 hour. All reactions had cleared by 24 hours. The irritancy effects to the respiratory system were not investigated.

Sensitisation
In a Guinea Pig Maximisation Test (GPMT) there was no evidence of reactions indicative of skin sensitisation to the notified chemical when tested using an induction topical concentration of 50% and a challenge concentration of 30% (the minimal irritating and maximum non-irritating concentrations, respectively). In an Open Epicutaneous Test (OET) the notified chemical demonstrated sensitisation potential when tested using an induction topical concentration of 30% and a challenge concentration of 30%. In a human repeat insult patch test conducted using a 5% solution of the notified chemical there were no reactions indicative of irritation or sensitisation observed in any of the 53 subjects.

The GPMT is generally considered to be the preferred Guinea Pig method, and was conducted in accordance with current OECD Guidelines, and GLP compliance. Therefore on a weight of evidence basis, considering the negative results obtained in both the GPMT and the HRIPT, the notified chemical is considered to not be classified as a skin sensitiser.

Phototoxicity
The notified chemical displayed primary irritancy potential but did not display phototoxic potential.

Repeat dose toxicity
The effect of repeated exposure to the notified chemical for 28 days was investigated in the rat at dose levels of 60, 300 and 1500 mg/kg/day. Significant toxic effects were observed in the high dose group, including sedation, leading to coma and death in 4/6 females, as well as associated adaptive effects (decrease in body weight gain, leukocytosis and reduced fibrinogen in males, and increased liver and

kidney weights). Sedation, as well as effects on liver weights were observed for animals in the mid dose group. The effects observed at the high and mid dose groups are considered to be treatment related and the sedative effects are considered adverse. A NOEL was established as 60 mg/kg bw/day, based on the absence of treatment-related effects at this dose level.

Genotoxicity
The notified chemical was not mutagenic to *E. Coli* or *S. Typhimurium*, and was not clastogenic to Chinese hamster V79 cells *in vitro*. However, in the *in vitro* chromosomal aberration test using Chinese hamster V79 cells there was evidence that the notified chemical may inhibit mitotic processes and induce numerical chromosome aberrations (increased rate of polyploid cells) and inhibit cell cycle progression (increased rate of cells with endoreduplicated chromosomes) in the absence of metabolic activation. No effects were seen in the presence of metabolic activation. The notified chemical did not cause chromosomal aberrations in mouse erythrocytes *in vivo*, and so is not considered to be an *in vivo* genotoxin.

Based on the available data the notified chemical is not classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

The highest occupational exposure is expected to occur to workers directly handling the imported fragrance mixture when it is added to the mixing vessel during formulation of the end-products. Based on EASE modelling the worst-case total systemic exposure (in the absence of PPE) is estimated as 0.044-0.33 mg/kg bw/day. A dermal NOEL was not determined, however a NOEL of 60 mg/kg bw/day was established in a 28-day oral study in the rat. The use of this NOEL results in a margin of exposure (MOE) of 182-1363. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. The MOE is based on conservative assumptions (100% dermal absorption, no PPE use) and likely overestimates the risk.

The notified chemical is not classified as a skin or eye irritant, but was found to be slightly irritating in the animal studies (including the phototoxicity and sensitisation studies). The risk of irritation effects in workers handling the notified chemical is expected to be low due to the low concentrations (maximum 5%) and the PPE expected to be worn.

The risk to transport and storage workers is expected to be low due to the negligible exposure expected.

The risk to workers using the end-products (cleaners, beauticians) is expected to be low based on the low exposure due to the low concentrations of notified chemical in the end-products.

6.3.2. Public health

The public may come into contact with the notified chemical (< 1%) through the use of a range of cosmetic and consumer products.

Systemic Toxicity
The worst -case long-term dermal exposure to the notified chemical is estimated as 0.127 mg/kg bw/day. A dermal NOEL was not determined, however a NOEL of 60 mg/kg bw/day was established in a 28-day oral study in the rat. The use of this NOEL results in a margin of exposure (MOE) of 472. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. The MOE is based on conservative assumptions (e.g. 100% dermal absorption) and likely overestimates the risk.
Therefore the risk to the public of systemic effects after the use of cosmetic products is considered to be minimal based on the known systemic toxicity of the notified chemical (non-genotoxic *in vivo*; MOE for chronic effects >100).

Local Toxicity
The public will be exposed to the chemical at a maximum concentration of 1%. Although slight

irritant effects were observed in some of the animal studies, at this concentration the risk of local irritancy effects is considered to be low.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical is imported and stored in a warehouse prior to delivery to the customer for reformulation. No release is anticipated at the notifier's storage facility and during distribution and transportation to customer sites, except in the event of an accident. In the event of a transport accident, the concentration of the notified chemical (<5%) in sealed containers would limit the release to the environment. Accidental spills of the notified chemical will be contained and the spilled chemical adsorbed on an inert support and disposed of to landfill.

Reformulation of the imported product into consumer products will be by the batch process where cleaning the blending equipment may result in the generation of waste waters containing the notified chemical. It is expected that most sites will have closed, automated mixing and dosing equipment. The quantity of notified chemical remaining in this wash water may be up to 1% of the import volume. The disposal route for these waste waters may include disposal to on-site waste water treatment plants and/or the sewer system. The quantity of notified chemical remaining in the emptied import containers may be up to 1% of the import volume. The disposal route for container rinsate may include on-site waste water treatment plants and/or the sewer system.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be used in household, laundry, and personal cleaning products. In these applications, it is anticipated that the entire product is eventually washed into the sewer system. The majority of the imported notified chemical (>98%) is therefore expected to be disposed of to sewers.

RELEASE OF CHEMICAL FROM DISPOSAL

It is anticipated that up to 1% of the notified chemical will be lost as residues in consumer containers, which are primarily sent to landfill or recycled.

7.1.2 Environmental fate

The notified chemical is moderately water soluble and is considered to be volatile. Its relatively high log Kow of 3.8 indicates that it is likely to partition to the soil or sediment. The notified chemical is considered not readily biodegradeable but inherently biodegradable. In landfill, the residue in the sludge is expected to degrade slowly by abiotic and biotic processes to oxides of carbon and water. For the details of the biodegradation studies please refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

It is anticipated that essentially all of the notified chemical (> 99%) will be released into the sewer system from the wash-off of products containing the chemical in domestic applications and clean-up of formulation equipment. As the notified chemical is to be used domestically, it is anticipated that release will occur on 365 days per year across Australia. The Predicted Environmental Concentration arising from this domestic release pattern was modelled using the SIMPLETREAT approach (EC 2003). The details of the calculation are presented below:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	180	kg/year
Proportion expected to be released to sewer	100	%
Annual quantity of chemical released to sewer	180	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	0.493	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	20.496	million
Removal within STP:		
(a) volatilisation	12	%
(b) Degradation	0	%
(c) Partition to sludge	20	%
(d) Remain in effluent	68	%
Daily effluent production:	4,099	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.08	µg/L
PEC - Ocean:	0.008	µg/L

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	Acute 96 h LC50 = 1.08 mg/L	Toxic
Daphnia Toxicity	Acute 48 h EC50 = 7.7 mg/L (CI: 6.27 - 10.21 mg/L)	Toxic
	Chronic 21 days NOEC = 0.71 mg/L	Slightly toxic
Algal Toxicity	72 h EbC50 = 8.4 mg/L	Harmful (based on 72 h ErC50)
	72 h ErC50 = 11 mg/L	

These results indicate that the notified chemical is toxic to aquatic organisms.

7.2.1 Predicted No-Effect Concentration

The Predicted No-Effect Concentration has been calculated from the most sensitive fish toxicity (96 h LC50 = 1.08 mg/L) of the notified chemical. As the results are available for three trophic levels, the assessment factor of 100 has been used.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
96 h LC50 for rainbow trout	1.08	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	10.8	µg/L

7.3. Environmental risk assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.08	10.8	**0.007**
Q - Ocean:	0.008	10.8	**0.0007**

The mitigated Risk Quotients are much less than 1 for both the river and ocean disposal scenarios. Therefore, the notified chemical is not expected to pose an unacceptable risk to the aquatic environment based on the current use pattern and at the current import volume.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical is not classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

and

As a comparison only, the classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	***Hazard statement***
Environment	Acute and Chronic II	toxic

Human health risk assessment
Under the conditions of the occupational settings described, the risk to workers is considered to be acceptable.

When used in the proposed manner the risk to the public is considered to be acceptable.

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.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - Avoid skin and eye contact

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Protective clothing
  - Safety glasses
  - Chemical-resistant gloves

  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 *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

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

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
  - the importation volume exceeds one tonne per annum notified chemical; or
  - the chemical is imported in fragrance mixtures at a concentration greater than 5%; or

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from aroma chemical in alcoholic perfumery, cosmetics, toiletries, household products, soaps, detergents and industrial perfumery, or is likely to change significantly;
  - the amount of chemical being introduced has increased from 0.18 tonnes, or is likely to increase, significantly;
  - if the chemical has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

Material Safety Data Sheet
The MSDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICO-CHEMICAL PROPERTIES

Freezing Point < -50°C

METHOD EC Directive 84/449/EEC A.1 Melting/Freezing Temperature.
Remarks No significant protocol deviations. GLP compliance
The test material continued to remain a liquid at -50 degrees C.
TEST FACILITY Givaudan-Roure SA (1993a)

Boiling Point 257°C at 101.3 kPa

METHOD OECD TG 104 Vapour Pressure.
92/69/EEC, A.4 (dynamic method).
Remarks The boiling point was estimated from the vapour pressure curve. (See Remarks on Vapour Pressure for further details). However, the study authors state that thermal stability tests (unspecified) show signs of instability in the notified chemical over 220° C.
TEST FACILITY Givaudan-Roure SA (1993b)

Density 953 kg/m^3 at 20°C

METHOD OECD TG 109 Density of Liquids and Solids.
Remarks The relative density was determined using an oscillating density meter. The oscillating density meter is calibrated periodically with distilled water and air. No significant protocol deviations. GLP compliance.
TEST FACILITY Givaudan-Roure SA (1993c)

Vapour Pressure 0.002 kPa at 20°C

METHOD OECD TG 104 Vapour Pressure.
92/69/EEC, A.4 (dynamic method).
Remarks The vapour pressure was determined by the dynamic method. The vapour pressure at 20°C was extrapolated from the temperature dependence of the vapour pressure of the notified chemical in the range 85.5 - 221°K (1 replicate). The system was calibrated using dodecane as a reference substance and appropriate corrections were applied to the measurements. GLP compliance.
TEST FACILITY Givaudan-Roure SA (1993b)

Water Solubility 0.04 g/L at 20°C

METHOD OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks The determination was carried out in triplicate using the Flask method. Based on the preliminary test, a saturated solution was obtained and placed in water bath at 30°C and stirred. After 24 h it was placed in water bath at 20°C to attain equilibrium. The undissolved materials were filtered. The concentration of the test material in the sample was determined by HPLC. GLP compliance.

It appeared rapid oxidation of the notified chemical to the acid form took place resulting in higher solubility of the substance.
TEST FACILITY Givaudan-Roure SA (1993d)

Hydrolysis as a Function of pH

METHOD OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$ <hours>*
4	25	710
7	25	620
9	25	2000

Remarks On the basis of the preliminary test at 50ºC, the hydrolysis test was performed at 25ºC at pH 4, 7 and 9 over 73 hours. The concentrations of the notified chemical were determined by HPLC. It appeared the results may be affected by the easy oxidizability of the test substance. GLP compliance.

TEST FACILITY Givaudan-Roure SA (1993e)

Partition Coefficient (n-octanol/water) log Pow = 3.8 at 20ºC

METHOD OECD TG 117 Partition Coefficient (n-octanol/water).

Remarks The HPLC method was used for the determination of partition coefficient. On the basis of the retention times of the seven references, the log Pow for the notified chemical was calculated. This compares with log Pow =3.7 calculated by the Fragment Method. GLP compliance.

TEST FACILITY Givaudan-Roure SA (1993f)

Fat (or n-octanol) Solubility Miscible in fat

METHOD OECD TG 116 Fat Solubility of Solid and Liquid Substances.

Remarks The notified chemical is miscible in all proportions with the standardised fat recommended in the guideline. All solutions were clear and homogeneous.

TEST FACILITY Givaudan-Roure SA (1993g)

Surface Tension 50 mN/m at 20°C

METHOD OECD TG 115 Surface Tension of Aqueous Solutions.
EC Directive 92/69/EEC A.5 Surface Tension.

Remarks This determination was carried out using a Krüss tensiometer type K6 and a procedure based on the Lecomte de Noüy method. No significant protocol deviations. The surface tension of the sample was measured at intervals and reported as the mean over a 21-minute period, corrected by interpolation from the Harkins-Jordan tables. As the surface tension is less than 60 mN/m, the notified chemical is considered to be surface active. GLP compliance.

TEST FACILITY RCC Notox B.V. (1993a)

Adsorption/Desorption log K_{oc} = 3.18

METHOD QSAR for non-hydrophobics as outlined in the EU TGD; Log Koc = 0.52 log Kow + 1.02)

Remarks The adsorption coefficient on soil was estimated from the octanol/water partition coefficient by QSAR (predominantly hydrophobic category).

Flash Point 68ºC at 101.3 kPa

METHOD (German Method DIN 51 758)

Remarks The flash point was determined by duplicate measurements using the Pensky-Martens closed cup tester method.
The apparatus used is a PMA 2 (Sommer und Runge KG, D-1000 Berlin). A brass cup is filled with the test substance to the mark, the lid is closed and the test substance is electrically heated in an aluminium oven at a controlled rate. The DIN programme is selected and the anticipated flash point introduced via the keyboard. The test proceeds automatically. The stirrer is activated and the sample is heated to 15ºC below the anticipated flash point. The heating rate is then adjusted to 3.5ºC per min. Then, at every 1ºC temperature increase, the stirrer is stopped, the glowing wire igniter is introduced at the aperture of the lid for one second and quickly removed, and the stirrer is started again. At the flash point, the ignited vapours above the liquid produce a sudden temperature increase which is detected by a fast response thermocouple. This freezes the temperature on the display and

stops the programme. The flash point can be read on the display.

TEST FACILITY Givaudan-Roure SA (1993f)

Autoignition Temperature 245°C

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).

Remarks No significant protocol deviations. GLP compliance.

TEST FACILITY RCC Notox B.V. (1993b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 401 Acute Oral Toxicity
Species/Strain	Rat/Ibm: RORO (SPF), also known as Fü-albino SPF rat
Vehicle	The notified chemical was suspended in Standard Suspending Vehicle (SSV) (1000 ml of SSV contains: 5 g sodium carboxy methyl cellulose of median viscosity, 4 ml Tween 80, 5 ml benzylalcohol, 9 g sodium chloride, dissolved in distilled water).
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5 male, 5 female	2000	0/5

LD50	>2000 mg/kg bw
Signs of Toxicity	No clinical symptoms were observed.
Effects in Organs	Body weight changes in both males and females were within the normal ranges. No autopsy findings were seen.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	F. Hoffman-La Roche & Co. Ltd (1988a)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	In-house method. GLP
Species/Strain	Rat/New Zealand White
Number of Animals	3 (2 males, 1 female)
Vehicle	None (tested as supplied)
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	The test method is similar to the OECD TG 404 Acute Dermal Irritation/Corrosion, except three animals were used concurrently rather than sequentially.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.67	0.33	0.67	2	< 72h	0
Oedema	0	0	0	0	NA	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal. NA, not applicable.

Remarks - Results	Well-defined erythema was noted at 2 treated sites at 1 hour after patch removal only. Very slight erythema was noted at all treated sites at 24 hour and on 2/3 treated sites at 48 hours after patch removal which returned to normal at 72 hours. Slight dryness was found in one of the test animals at 72-hour observation only.
CONCLUSION	The notified chemical is slightly irritating to the skin.

TEST FACILITY	Inveresk Research International (1988)

B.3. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (2 males, 1 female)
Observation Period	72 hours
Remarks - Method	No significant protocol deviations
RESULTS	Slight erythema and oedema in conjunctiva and visible vessels in sclera in all test animals and slight discharge in 2/3 animals were observed 1 hour after treatment, but all reactions had disappeared by 24 hours. No mortality, clinical symptoms or abnormal necropsy findings were seen. Body weight gain of all test animals was within the normal range.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Research and Consulting Co. AG (1990)

B.4. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – Guinea Pig Maximization Test EC Directive 96/54/EC B.6 Skin Sensitisation.
Species/Strain	Guinea pig/Himalayan White spotted
PRELIMINARY STUDY	Minimum Irritating Concentration (for use in induction phase): intradermal: 0.5% in ethanol topical: 50% in ethanol Maximum Non-irritating Concentration (for use in challenge phase): topical: 30% in ethanol
Signs of Irritation	With intradermal injection, slight to well-defined erythema and oedema were observed in 2 test animals (1 male and 1 female) at all doses tested (from 0.1% to 5%). With topical application, slight erythema was seen in some test animals immediately and 24 hours after applications, but disappeared by 48 hours.
MAIN STUDY	
Number of Animals	Test Group: 10/sex Control Group: 5/sex
INDUCTION PHASE	Induction Concentration: intradermal: 0.5% in ethanol topical: 50% in ethanol
Signs of Irritation	For both control and treated animals the application area around the injection sites showed oedema (from day 2 to 5), erythema (from day 2 to 6), necroses (from day 7 to 14), and exfoliation (from day 15 to 25) in both control and test group animals.
CHALLENGE PHASE	
1st challenge	topical: 30% in ethanol
2nd challenge	Not performed based on the result observed after the 1st challenge test.
Remarks - Method	No significant protocol deviations.
RESULTS	Slight erythema was observed in 3/20 animals immediately and 1/20 (5%)

24 hours after the first challenge. No skin reactions were found in control group.

No mortality, clinical symptoms or abnormal necropsy findings were seen. Body weight changes of all test animals were within the normal range, except reduced body weight in one control animal at the end of test.

CONCLUSION — There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY — Research and Consulting Co. AG (1988a)

B.5. Skin sensitisation

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 406 Skin Sensitisation – Open Epicutaneous Test (1981 Guideline)

Species/Strain — Guinea pig/Himalayan White spotted

PRELIMINARY STUDY — Maximum Non-irritating Concentration:
topical: 30% in ethanol

MAIN STUDY

Number of Animals — Test Groups: 3/sex/group (total: 24) Control Group: 3 male, 3 female

INDUCTION PHASE — Induction Concentration:
topical: 3%, 10% and 30% in ethanol , and 100%

Signs of Irritation — Slight to moderate irritation was reported in animals receiving 30% of the notified chemical. Slight to severe irritation was reported in animals receiving 100% of the notified chemical.

CHALLENGE PHASE

1st challenge — topical: 1%, 3%, 10% and 30% in ethanol

2nd challenge — topical: 1%, 3%, 10% and 30% in ethanol

Remarks - Method — The Open Epicutaneous Test (OET) is no longer an OECD Guideline Test (it was removed when the Guideline was rewritten in 1992 to give preference to the GPMT and Buehler tests).

The OET method involves application of 0.1 mL of test solution to the same area of clipped skin of guinea pigs 5 days per week, for 4 weeks. There were 5 test groups receiving different concentrations of the test material (0%, 3%, 10%, 30% and 100%). After a rest period of 7 days the contralateral flanks of all the guinea pigs were treated with the test article at 4 application sites (1, 3, 10 and 30% test article). The reactions were read at 24, 48 and 72 hours. A second challenge phase was conducted in a similar manner 7 days later.

RESULTS

First challenge (Day 36) – Results evaluated 24 hrs after application

Group	Induction Concentration (%)	Challenge Concentration (%) Positive/Total animals			
		1%	3%	10%	30%
1	0	0/6	0/6	0/6	0/6
2	3	0/6	0/6	0/6	0/6
3	10	0/6	0/6	0/6	1/6
4	30	0/6	0/6	2/6	2/6
5	100	0/5*	0/5	2/5	3/5

*One animal in Group 5 died spontaneously on Day 3

Second challenge (Day 43) – Results evaluated 24 hrs after application

Group	Induction Concentration	Challenge Concentration (%) Positive/Total animals

	(%)	1%	3%	10%	30%
1	0	0/6	0/6	0/6	0/6
2	3	0/6	0/6	0/6	0/6
3	10	0/6	0/6	0/6	0/6
4	30	0/6	0/6	0/6	2/6
5	100	0/5*	0/5	2/5	2/5

*One animal in Group 5 died spontaneously on Day 3

Remarks - Results

Group 3(Induction with 10% of the notified chemical):
After first challenge, 1/6 animals displayed slight erythema 24 hours after challenge with 30% of the notified chemical. However, there were no reactions observed at 48 hrs or 72 hrs after the first challenge, or in the second challenge.

Group 4(Induction with 30% of the notified chemical):
After the first challenge, 2/6 animals displayed slight erythema at 24hrs after challenge with 10% and 30% of the notified chemical, persisting to 72 hrs at the site where 30% of the notified chemical was applied. After the second challenge, 2/6 animals displayed slight erythema 24 hrs after challenge with 30% of the notified chemical, persisting to 72 hrs in one animal.

Group 5(Induction with 100% of the notified chemical):
After the first challenge, 3/5 animals displayed slight to moderate erythema 24 hours after challenge with 10% and 30% of the notified chemical, with slight erythema persisting in 2/5 animals 72 hours after challenge. After the second challenge, 2/5 animals displayed slight erythema 24 hours after challenge with 10% and 30% of the notified chemical, with slight erythema persisting to 72 hours at the site where 30% of the notified chemical was applied.

No skin reactions were found in Group 1 (control group) or Group 2 (induction with 3% notified chemical).

Body weight changes of all test animals were within the normal range. One female in the group inducted with 100% of the notified chemical died spontaneously on day 3, after application of the test article.

CONCLUSION

The notified chemical demonstrated sensitisation potential at a concentration of 30% under the test conditions.

TEST FACILITY

Research and Consulting Co. AG (1988b)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE

Notified chemical

METHOD

Human Repeated Insult Patch Test (In-house method)

Study Design

Induction Procedure:
Occlusive patches applied to the back of each subject for 24 hours, with 9 repeated applications. 24 hours rest periods followed the Tuesday and Thursday removals and 48 hours followed the Saturday removal.

Rest Period: 10 to 21 days

Challenge Procedure: the challenge patch was applied to a previously unpatched site for 24 hours which were observed 24 and 48 hours after application.

Study Group

53 subjects (11 males, 42 females) - non-exclusive panel

Vehicle	Dimethyl Phthalate C-58192
Remarks - Method	5% of the notified chemical in vehicle was tested.
RESULTS	A single transient and non-specific patch test response was observed in 1/53 test subjects during the challenge phase at 48-hour, but disappeared by 72 hours. This was not considered to be an irritant or allergic reaction.
CONCLUSION	A Repeated Insult Patch Test was conducted using the notified chemical diluted with Dimethyl Phthalate C-58192 to 5% under occlusive dressing. The notified chemical was non-irritating and non-sensitising under the conditions of the test.
TEST FACILITY	Essex Testing Clinic (1989)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat, outbred stock. Ibm: RORO (SPF) or Fü-albino.
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Standard Suspending Vehicle (SSV) (1000 ml of SSV contains: 5 g sodium carboxy methyl cellulose, 4 ml Tween 80, 5 ml benzyl alcohol, 9 g sodium chloride, dissolved in distilled water).
Remarks - Method	The protocol deviations were: - Functional observations were not included (study was conducted before the OECD Guideline was updated to include these) - The weights of the following organs were not recorded: epididymides, thymus, spleen, brain, heart - Tissue samples of the following organs were not examined: spinal cord, thymus, thyroid, urinary bladder, lymph nodes, peripheral nerve, bone marrow.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	6male, 6 female	0	0
low dose	6male, 6 female	60	1 male*, 1 female*
mid dose	6male, 6 female	300	1 female*
high dose	6male, 6 female	1500	4 female

* Accidental deaths due to aspiration of the test article into the lungs.

Mortality and Time to Death

Two females of the high-dose group were found in a deeply comatose and moribund state on the morning of Day 2 of the study. They were euthanized for humane reasons. Two further females of the high-dose group were found in similar states in the afternoon of Day 2 and were also euthanized.

Three accidental mortalities (1 male and 1 female of the low dose group; 1 female of the mid dose group) occurred due to aspiration of the test article into the lungs followed by alveolar haemorrhage and oedema. These mortalities due to aspiration were not related to the toxicity of the test substance.

Clinical Observations

Slight sedation was noted in all animals in the high-dose group starting 10-15 minutes after test article intake in both sexes.

Slight sedation was noted in one female and one female in the mid-dose group on the second and third day of gavage, respectively, starting 30-40 minutes after administration and lasting up to one hour.

A statistically significant decrease in body weight gain was observed for males in the high dose group. Comparison to the female high dose group was not possible due to the high incidence of mortality.

Laboratory Findings
Clinical Chemistry
The measured values generally remained within the physiological range. A statistically significant decrease of total protein was noticed in the male high-dose group. However, the decreased levels remained within the normal range. A similar decrease, but without statistical significance was also seen in surviving females of the high-dose group.

Haematology
Statistically significant changes in the mean leukocyte count and fibrinogen levels were observed in high-dose males. Comparison to the female high-dose group was not possible due to the high incidence of mortality.

Effects in Organs
Macroscopic findings
Statistically significant increases in the absolute and relative liver weights in the male and female high-dose and mid-dose groups were observed. Increases in the relative kidney weight of the male and female high-dose groups were also observed.

Microscopic findings
No histological alterations were found which could be attributed to treatment (except the alveolar haemorrhage and oedema which was caused by accidental aspiration of the test article into the lungs).

Remarks – Results
Significant toxic effects were observed in the high dose group, including sedation, leading to coma and death in 4/6 females. Sedation, as well as effects on liver weights were observed for animals in the mid dose group. The effects observed at the high and mid dose groups are considered to be both treatment related and adverse. No treatment related effects were observed at the low dose level (60 mg/kg bw/day).

CONCLUSION
The No Observed Effect Level (NOEL) was established as 60 mg/kg bw/day in this study, based on the absence of treatment-related effects at this dose level.

TEST FACILITY	F.Hoffman-La Roche Ltd (1991a)

B.7a. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	In-house method. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100
Metabolic Activation System	Aroclor 1254 induced male rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 0.001, 0.01, 0.025, 0.05, 0.1, 0.25, 0.5 µl/plate b) Without metabolic activation: 0.0005, 0.001, 0.01, 0.025, 0.05, 0.1, 0.25 µl/plate
Vehicle	DMSO for all strains except for TA-1535, TA-100 without activation where water was used.
Remarks - Method	Similar to OECD Guideline 471 Bacterial Reverse Mutation Test. The preliminary study was conducted using tester strain TA100 with a range of doses 0.018 to 150 µg per plate. Positive controls used: -S9: Sodium Azide used with TA-1535, TA-100. 2-Nitrofluorene used with TA-1538, TA-98. Quinacrine mustard used with TA-1537. +S9: 2-Aminoanthracene.

RESULTS

Metabolic Activation	*Test Substance Concentration (µl/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	0.073	0.25	> 0.25	Negative
Test 2		0.25	> 0.25	Negative
Present				
Test 1	0.146	0.5	> 0.5	Negative
Test 2		0.5	> 0.5	Negative

Remarks - Results: The test substance did not cause an increase in the number of revertants per plate for any of the tester strains, with or without metabolic activation. Positive controls confirmed the sensitivity of the test system.

CONCLUSION: The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY: Hazelton Laboratories America, Inc. (1989)

B.7b. Genotoxicity – bacteria

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure (Test 1), Pre incubation procedure (Test 2)

Species/Strain: *E. coli*: WP2uvrA

Metabolic Activation System: Phenobarbitone/β-naphthoflavone-induced rat liver S9 mix.

Concentration Range in Main Test: a) With metabolic activation: 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate
b) Without metabolic activation: 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate

Vehicle: Ethanol

Remarks - Method: The preliminary toxicity test became Test 1 since the results gave evaluable plates at five concentrations or more.
Positive controls used:
-S9: Methylmethane sulfonate
+S9: 2-aminoanthracene

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	1000	> 5000	Negative
Test 2	-	> 5000	> 5000	Negative
Present				
Test 1	-	333	> 5000	Negative
Test 2	-	5000	2500	Negative

Remarks - Results: No substantial increase in revertant colony members was observed following treatment with the test substance. Positive controls confirmed the sensitivity of the system.

CONCLUSION: The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY Research and Consulting Co. AG (2006)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2000/32/EC B.17 Mutagenicity - In vitro Mammalian Cell Gene Mutation Test.

Species/Cell Line: Chinese hamster V79 cells
Metabolic Activation System: S9 fraction from Phenobarbital/β-flavone induced rat liver
Vehicle: Ethanol
Remarks - Method: Deviation from the study protocol was as follows: During analysis of the metaphase, only metaphases with 22 +/- 1 were included in the analysis. The mitotic index (% cells in mitosis) was determined to describe the cytotoxic effect. The number of polyploid cells in 500 metaphase cells per culture were determined (% polyploid metaphases). The number of endomitotic cells scored at the evaluation of polypoid cells was noticed and reported (% endomitotic metaphases). The deviations are not anticipated to effect the outcome of the study.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	6.3, 12.5, 25.0*, 37.5*, 50.0*, 75.0	4 hrs	18 hrs
Test 2a	0.47*, 0.94*, 1.88*, 3.75, 7.5, 15.0	18 hrs	18 hrs
Test 2b	0.23, 0.47, 0.94, 1.88, 3.75*, 7.5	28 hrs	28 hrs
Present			
Test 1	37.5, 75.0*, 100.0*, 150.0*, 200.0, 250.0	4 hrs	18 hrs
Test 2	37.5*, 75.0*, 100.0*, 150.0, 200.0, 250.0	4 hrs	28 hrs

* cultures selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	*Cytotoxicity in Preliminary Test**	*Cytotoxicity in Main Test**	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	60.9	75	> 7.5	negative
Test 2a	30.5	7.5	> 15.0	negative
Test 2b		> 7.5	> 7.5	negative
Present				
Test 1	243.8	150.0	> 250	negative
Test 2		150.0	> 250	negative

* Based on > 50% reduction in cell numbers

Remarks - Results: The structural aberration rates of cells after treatment with the test item (0.5 – 4.0% aberrant cells, exclusive of gaps) were close to the range of solvent control values (0.5 – 3.5% aberrant cells, exclusive of gaps) and within the range of historical control data (0.0 – 4.0% aberrant cells, exclusive of gaps).

In Experiment 1, in the presence of S9 mix a slight increase in the number of cells carrying exchanges (2.5%) was observed after 4 hrs treatment with 150 µg/mL. However, the single value slightly exceeding historical control data range (0.0 – 2.0% aberrant cells with exchanges) was regarded as biologically irrelevant.

In Experiment 1 in the absence of S9 mix, a relevant increase of endomitotic cells indicating that the test item influences the cell cycle progression of the cells was observed after treatments with 37.5 and 50.0 µg/mL (3.1% and 1.4%, respectively). In the presence of the S9 mix, the values of the test item groups (0.2 – 0.4% endomitotic metaphases) were close to the range of the respective control values (0.1 – 0.2% endomitotic metaphases), and were regarded as biologically irrelevant.

In Experiment 1, in the absence and the presence of S9 mix, in Experiment 2 after 18 hrs treatment in the absence of S9 mix and in Experiment 2 in the presence of S9 mix, no biologically relevant increase in the rate of polyploid metaphases was found after treatment with the test item (1.4 – 5.6%) compared to the rates of solvent controls (1.5 – 3.6%).
In Experiment 2, in the absence of S9 mix, at the 28 hrs preparation interval, after treatment with 3.75 µg/mL an increase in the frequencies of polyploid metaphases (7%) close to the borderline of the historical control data range (0.0 – 8.5% polyploid cells) was observed. At the pre-check of the slides for scoring for the evaluation of cytogenetic damage increased numbers of polyploid cells were observed but not quantified. The next higher concentration (7.5 µg/mL) was scored to corroborate the observation at 3.75 µg/mL. A relevant increase (19.8% polyploid cells) exceeding the historical control data range (0.0 – 8.5% polyploid cells) was observed. This finding indicated that the test item may inhibit the mitotic processes and induce numerical chromosome aberrations.

In both experiments, EMS (400 and 400 µg/mL, respectively) and CPA (0.7 and 1.0 µg/mL, respectively) were used as positive controls and showed distinct increases in cells with structural chromosome aberrations.

CONCLUSION

The notified chemical was not clastogenic to Chinese hamster V79 cells treated in vitro under the conditions of the test. However, the notified chemical may inhibit mitotic processes and induce numerical chromosome aberrations (increased rate of polyploid cells) and inhibit cell cycle progression (increased rate of cells with endoreduplicated chromosomes) in the absence of metabolic activation.

TEST FACILITY

Research and Consulting Co. AG (2005)

B.9. Genotoxicity – in vivo

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test.

Species/Strain	Füllinsdorf Moro Albino mice
Route of Administration	Oral – gavage
Vehicle	Standard Suspension Vehicle (SSV) (1000 ml of SSV contains: 5 g sodium carboxy methyl cellulose, 4 ml Tween 80, 5 ml benzyl alcohol, 9 g sodium chloride, dissolved in distilled water).
Remarks - Method	No significant protocol deviations. Animals received a single oral dose by gavage.

Dose-range finding assays were conducted from doses ranging from 2000 to 6000 mg/kg. All animals treated with 5000 or 6000 mg/kg died. 1/3 animals died after treatment with 3000 or 4000 mg/kg. No mortalities were reported in animals treated with 2000 mg/kg, therefore this dose was chosen as the high dose for the main experiment.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
vehicle control	6/sex/sacrifice time	0	24, 48, 72 hrs
low dose	6/sex	1000	24 hrs
high dose	6/sex/sacrifice time	2000	24, 48, 72 hrs
positive control, P	6/sex	50	24 hrs

P = Procarbazine hydrochloride

RESULTS

Doses Producing Toxicity	3/36 mice treated with 2000 mg/kg died. However, no indication of bone marrow toxicity demonstrated by a reduction of the PCE/NCE ratio was observed.
Genotoxic Effects	The notified chemical did not induce a statistically significant increase in the frequency of micronucleated PCEs.
Remarks - Results	The notified chemical is considered negative in the mouse bone marrow micronucleus assay under the conditions of this assay. Although there was no indication of bone marrow toxicity (i.e. no decrease in the PCE:NCE ratio) the oral bioavailability of the test substance was evidenced by the 3 deaths observed. The positive control demonstrated the sensitivity of the test and the negative controls were within historical limits.

CONCLUSION — The notified chemical was not clastogenic in this in vivo mouse bone marrow micronucleus assay under the conditions of the test.

TEST FACILITY — F.Hoffman-La Roche Ltd (1991b)

B.10. Phototoxicity

TEST SUBSTANCE — Notified chemical

METHOD — Not specified

Study Group	10 Himalayan white spotted guinea pigs (5 males, 5 females)
Vehicle	Ethanol incorporating approximately 2% DMSO to enhance skin penetration
Remarks - Method	The test animals were sedated and narcotized by intraperitoneal injection. Both flanks of the animals were shaved and 4 test sites (2 cm^2) on each side were marked with a circular stamp. 0.025 ml solutions containing the test substance at concentrations of 3%, 10% and 30% as well as test samples were applied to 3 test sites. The 4^{th} test site was treated with 0.1% alcoholic solution of 8-Methoxypsoralen (8-MOP), used as a positive control. 30 mins after application, the left flank of the animals was exposed to non-erythemogenic UV-A radiation (20J/cm^2). Test sites on the right flank of the animals remained unexposed and serve as control sites. Animals were examined 24 hours, 48 hours and 72 hours after application of the test material for signs of erythema and oedema.

RESULTS

Remarks - Results

24 hours after exposure, slight erythema was observed on both left (irradiated) and right flanks of 7/10 animals at the site treated with 30% of the notified chemical. This reduced to 3/10 animals 48 hours after exposure and 2/10 animals 72 hours after exposure. The frequency and intensity of skin reactions on the left side exposed to radiation were the same as skin reactions on the right side which was not exposed to radiation.

No skin reactions were observed at the sites treated with 10% and 3% of the notified chemical.

Well-defined to moderate erythema was observed at the radiated skin sites treated with 0.1% MOP (positive control), confirming the sensitivity of the test

system.

CONCLUSION	The notified chemical displayed primary irritancy potential but did not display phototoxic potential.
TEST FACILITY	F.Hoffman-La Roche Ltd (1988b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I).
Inoculum	Activated sludge from a biological water treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	None
Remarks - Method	The test substance was tested in duplicate at a nominal test concentration of 100 mg/L for up to 28 days. The test consisted of the inoculum control, reference substance, aniline at 100 mg/L and the toxicity control containing the test substance, reference substance and inoculum. The consumption of oxygen was measured using respirometer and the evolved CO_2 was absorbed in soda lime. The amount of O_2 consumed was expressed as % of ThOD calculated from the molecular formulae. The pHs were measured during the test.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	-5	7	81
14	-8	14	82
21	-9	21	83
28	-9	28	84

Remarks - Results	The degradation of the test substance after 28 days was negative, indicating a slight toxic effect to the inoculum. A slight toxic effect was observed in aniline in the presence of the test substance for the first 24 days in the toxicity control. Degradation of the aniline exceeded 81% after 7 days and 82% after 14 days and thus validating the test results. The pHs were within the acceptable range.
CONCLUSION	The test substance is not considered to be ready biodegradable.
TEST FACILITY	Givaudan-Roure SA (1993i)

C.1.2. Bioaccumulation

Given the low molecular weight and the relatively high log Kow of 3.8, the notified chemical has the potential to bioaccumulate. However, it is inherently biodegradable and will be widely dispersed at very low concentration.

C.1.3. Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302 C - Inherent biodegradability: Modified MITI test II
Inoculum	Activated sludge from a biological water treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	None
Remarks – Method	The test substance was tested in duplicates at nominal test concentration of 30 mg/L with inoculum control for up to 28 days. The consumption of

oxygen was measured by respirometer and the evolved CO_2 was absorbed in soda lime. The amount of O_2 consumed was expressed as % of ThOD calculated from the molecular formulae. The pH was measured during the test. The reference test was based on the ready biodegradation test above for the same activated sludge.

RESULTS

Test substance	
Day	*% Degradation*
7	18
14	28
21	76
28	104

Remarks – Results: The biodegradation of the test substance after 28 days was 100%. At the test concentration of 30 mg, no toxic effect on the micro-organisms was observed. pHs were within the acceptable limit.

CONCLUSION: The test substance is considered to be inherently biodegradable.

TEST FACILITY: Givaudan-Roure SA (1993j)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test – Semi-static conditions
EC Directive 84/449/EEC C.1 Acute Toxicity for Fish – Semi-static conditions

Species	Rainbow trout (*Salmo gairdneri*)
Exposure Period	96 h
Auxiliary Solvent	Acetone
Water Hardness	Total Hardness: 41.8 fr.Hº
Analytical Monitoring	HPLC
Remarks – Method	Groups of 10 fish were exposed to the controls with and without acetone and nominal test concentrations of 8.00, 4.44, 2.47, 1.37 and 0.76 mg/L for a period of 96 h. Every 24 h the fish were transferred to freshly prepared test media. Mortality of the fish were observed daily. Swimming behaviour, respiratory rate, haemorrhage, exophthalmus, mycoid discharge, flatulence, pigmentation and snapping at the surface were recorded at 2, 24, 48, 72 and 96 h after treatment. pHs, temperatures and dissolved oxygen were monitored during the test.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
*0	*0	10	0	0	0	0	0
**0	**0	10	0	0	0	0	0
0.76	0.45	10	0	0	0	0	0
1.37	0.80	10	0	5	5	5	5
2.47	1.45	10	2	5	5	5	6
4.44	2.6	10	6	8	8	9	9
8.00	4.69	10	8	10	10	10	10

*Control without acetone
**Control with acetone

LC50: 1.08 mg/L at 96 hours.

NOEC	0.047 mg/L at 96 hours.
Remarks – Results	All values were expressed as actual concentrations. pHs, temperatures and dissolved oxygen were within acceptable range. The concentrations of the test substance was <80% of the nominal values. Therefore, all values were estimated as actual concentrations using the mean measured concentration (58.6%). No mortality was observed in the controls. A mortality rate of 50% was observed at 0.80 mg/L (measured value) and 60% at 1.45 mg/L (measured value). At nominal concentration of 8 mg/L, the mortality was 100% within 24 h of exposure.
CONCLUSION	The test substance is considered to be toxic to fish.
TEST FACILITY	Givaudan-Roure SA (1991a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Semi-static conditions (OECD-Immobilisation Test). EC Directive 84/449/EEC C.2 Acute Toxicity for Daphnia – Semi-static condition
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Acetone
Water Hardness	Not stated
Analytical Monitoring	HPLC
Remarks - Method	The test was performed at nominal test concentrations of 0.625–10 mg/L. Untreated samples with and without acetone were used as controls. 10 daphnids were exposed to each test concentration. All test were run in duplicate. During exposure, the animals were kept at 19.5ºC with 16 h of illumination. After 24 h of exposure, the daphnids were transferred into freshly prepared solutions. The mobility of the daphnids was observed at 24 and 48 h. pH and dissolved oxygen were monitored during the test. A separate test with reference compound potassium dichromate was performed. The EC values were estimated by using the Logit-model. The concentrations of the test substance were measured at the beginning and after 24 h of the test.

RESULTS

Concentration mg/L Nominal	*Number of D. magna*	*% Immobilised*	
		24 h	*48 h*
0, 0*	10, 10	0, 0	0, 0
0, 0**	10, 10	0, 0	0, 0
0.625, 0.625	10, 10	0, 0	0, 0
1.25, 1.25	10, 10	0, 0	0, 0
2.5, 2.5	10, 10	0, 0	0#, 0#
5, 5	10, 10	0, 0	30#, 10#
10, 10	10, 10	30, 0	60#, 80#

* Control without acetone
** Control with acetone
# used for Logit estimation

LC50	7.7 mg/L at 48 hours (CI 95%: 6.27–10.21 mg/L)
NOEC	2.76 mg/L at 48 hours
Remarks - Results	Temperatures and pH were within the acceptable limits. The nominal concentrations of 0.625, 2.5 and 10 mg/L were found to be 72.2, 48.7 and 30.5% of the nominal values after 24 h, respectively. No immobilisation

was observed with the controls and at the nominal concentration of 2.5 mg/L and below. Immobilisation was observed at a nominal concentration of 5 mg/L. The tests were validated by the reference compound potassium dichromate with 48 h EC50 of 1.25 mg/L.

CONCLUSION — The test substance is considered to be toxic to *Daphnia magna*.

TEST FACILITY — RCC Limited (1991b)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 211 *Daphnia magna* Reproduction Test – Semi-static condition

Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	Acetone
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	On the basis of range finding test, the test was performed at the nominal test concentrations of 0.38, 0.12, 0.38 1.2 and 3.8 mg/L. In this semi static test, the test media were renewed on days 2, 5, 7, 9, 12, 14, 16 and 19 of the exposure period. The mortality of adults and the number of young were recorded at the start of the test, at the first and second day of the test and thereafter 3 times per week before renewal of test media. The reproduction rate was calculated as the total number of living offspring produced per parent female alive at the end of the test. The EC50 of the reproduction rate was calculated by linear interpolation. The test was performed at water temperature of 20-22ºC during the test period. pH and dissolved oxygen were monitored during the test.

RESULTS

Concentration mg/L *Nominal*	*Number of D. magna*	*Number of surviving test animals* *14 d*	*21 d*
Control (0)	10	10	8
0.038	10	9	9
0.12	10	9	9
0.38	10	9	9
1.2	10	10	10
3.8	10	9	9

Concentration mg/L *Nominal* *Actual*	*The total number of alive, young daphnids (cumulative values) by all adults* *14 d*	*21 d*
Control	214	635
0.038	227	648
0.12	178	589
0.38	219	539
1.2	226	625
3.8	20	80

EC50 (reproduction rate)	1.7 mg/L at 21 days (mean measured value)
NOEC	0.71 mg/L at 21 days (mean measured value)
Remarks - Results	pH and dissolved oxygen were within acceptable limit. The measured test concentrations for nominal concentrations of 1.2 and 3.8 mg/L varied in the range of 75-81% of the nominal values at the start of the test. The slightly reduced values could be due to the oxidation of the test item. In

the stability control samples, the mean test item concentrations had further decreased to 29-58% of the nominal values. The biological results were based on the mean measured test concentrations. The mean measured concentrations were 0.71 and 2.6 mg/L for nominal concentrations of 1.2 and 3.8 mg/L, respectively.

Taking into account the survival rates and the reproduction rates of the test animals, no toxic effects were observed at the measured concentration of 0.71 mg/L and below and toxic effects were observed at the measured concentration of 2.6 mg/L.

CONCLUSION	The test substance is considered to be harmful to *Daphnia magna*
TEST FACILITY	RCC Limited (2002)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	Green alga (*Scenedesmus subspicatus*)
Exposure Period	72 hours
Concentration Range	Nominal: 0.46, 1.0, 2.2, 4.6, 10 and 22 mg/L
Auxiliary Solvent	None
Water Hardness	Not stated
Analytical Monitoring	HPLC
Remarks - Method	On the basis of range finding test, a definitive test consisted of nominal test concentrations in the range of 0.46 – 22 mg/L were used in the test. The test included 3 replicates per test concentrations and 6 replicates in the control for a duration of 72 h under a static and non-renewal exposure system. The algae cell densities were determined by electronic particle counter and the shape of the algal cells was microscopically examined. pH and temperatures were recorded during the test. The EC10, EC50 and EC90 were calculated by Probit Analysis.

RESULTS

Biomass		*Growth*	
Eb50 *mg/L at 72 h (measured value)*	*NOEC* *mg/L (measured value)*	*ErC50* *mg/L at 72 h (measured value)*	*NOEC* *mg/L (measured value)*
8.4	3.2	11 (CI: 7.4-20)	3.2

Remarks - Results	The temperature and pH were within acceptable range. The mean measured test concentrations at the start of the test ranged from 72-79% of the nominal values. At the end of the test 67-78% of the nominal values were found. The losses at the start of the test could be due to oxidation of the test item during the preparation of the samples. The total mean measured test concentrations varied in the range of 69-79% of the nominal values. Therefore, the biological results were based on the mean measured values. The biological results of the nominal test concentrations 0.46, 1.0 and 2.2 mg/L were not taken into account at the Probit Analysis as these values were below the 72 h NOEC value of 3.2 mg/L. Significant inhibition effects on the biomass and growth rate were observed at the measured concentration of 7.2 mg/L (nominal concentration of 10 mg/L) and no significant effects were observed at the mean measured concentration of up to 3.2 mg/L.

CONCLUSION	The test substance is considered to be harmful to alga.
TEST FACILITY	RCC Limited (1999)

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