File No: LTD/1740

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Chemical in Irgazin Rubine L 4030

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (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 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.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This 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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SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1740	BASF Australia Ltd	Chemical in Irgazin Rubine L 4030	No	≤ 1 tonne per annum	Component of automotive refinish paints

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

Human health risk assessment
Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment

On the basis of the assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Local exhaust ventilation during spray application

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid inhalation of spray particles

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Coveralls, safety glasses, impervious gloves

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

- Spray applications should be carried out in accordance with the Safe Work Australia Code of Practice for *Spray Painting and Powder Coating* (SWA, 2012) or relevant State or Territory Code of Practice.

Disposal

- Where reuse or recycling are not available or practical, dispose of the chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, physical 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(2) of the Act; if
  - the function or use of the chemical has changed from component of automotive refinish paints, or is likely to change significantly;
  - the amount of chemical being introduced has increased, or is likely to increase, significantly;
  - 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 (M)SDS of the notified chemical (and products containing the notified chemical) provided by the notifier were reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
BASF Australia Ltd (ABN: 62 008 437 867)
Level 12, 28 Freshwater place
SOUTHBANK VIC 3006

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year) – Similar to a chemical that has been previously assessed by NICNAS.

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity/impurities, use details and import volume.

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)
None

NOTIFICATION IN OTHER COUNTRIES
USA

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
QAVR Additive N-7635 Dry
Irgazin Rubine L 4030 (product containing approx. 4% of notified chemical)

MOLECULAR WEIGHT
UVCB, molecular weight generally < 500 Da.

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

3. COMPOSITION

DEGREE OF PURITY
Chemical is a multi-component reaction mixture.

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Dark red powder

Property	Value	Data Source/Justification
Melting Point	> 300 °C	Measured
Boiling Point	Not determined	Expected to be very high, based on melting point
Density	1370 kg/m^3 at 22°C	Measured
Vapour Pressure	Not determined	Expected to be very low, based on melting point
Water Solubility	1.0×10^{-4} g/L at 20 °C	Measured (OECD TG 105)
Hydrolysis as a Function of	Not determined	Due to the low water solubility no

pH		significant hydrolysis is expected in the environment
Partition Coefficient (n-octanol/water)	log Pow = 5.76 at 25 °C	Calculated (fragment method, OECD TG 117)
Adsorption/Desorption	Not determined	The notified chemical is expected to have potential to adsorb to sediment sludge from water based on the low water solubility
Dissociation Constant	pKa = 3, 0.3	Estimated based on the structural information
Surface Tension[+]	62.2-64.4 mN/m at 20 °C	Measured
Particle Size	Inhalable fraction (< 100 μm): approx. 95% Respirable fraction (< 10 μm): 24-33% MMAD * = 20.4 μm	Measured
Flash Point	Not determined	Not applicable for solid material
Autoignition Temperature	260 °C	Measured
Explosive Properties	Not considered to have explosive properties	Measured
Oxidising Properties	Not considered to have oxidising properties	Measured

* MMAD = Mass Median Aerodynamic Diameter
[+] New study (refer to Appendix A for details)

DISCUSSION OF PROPERTIES
The following tests carried out for explosive properties were negative: thermal sensitivity, mechanical sensitivity (shock) and mechanical sensitivity (friction).

Reactivity
The notified chemical is expected to be stable under normal conditions of use.

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

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 automotive refinish paints.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	<1	<1	<1	<1	<1

PORT OF ENTRY
Melbourne and Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Notifier

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of automotive refinish paints in 1L and 3.5L tin cans packed in fibreboard cartons and shrink wrapped in wooden pallets. The pallets of cartons will be transported by road for storage at contracted warehouses.

USE
The notified chemical will be used as a component of automotive refinish paints at a concentration of ≤ 0.5%.

OPERATION DESCRIPTION
There will be no reformulation or repackaging of products containing the notified chemical in Australia.

End-use
The imported automotive paints containing the notified chemical at up to 0.5% concentration will be used at automotive refinish sites. Paint products will be prepared by stirring, transferring and dilution and will be applied to automobiles, predominantly by spray painting conducted in a dedicated spray booth with downdraft ventilation. However touch-up applications may also be performed using paint brushes under ventilation.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	1-2	10-20
Warehouse	1-2	10-20
End-use	1-2	50-100

EXPOSURE DETAILS
Transport and storage workers may come in contact with the notified chemical as a component of automotive paints at up to 0.5% concentration only in the event of accidental rupture of containers.

Dermal and ocular exposure to the notified chemical (≤ 0.5%) may occur during weighing, mixing and transfer of the automotive paint, and application of touch-up paint by brush. The notifier states that exposure to the notified chemical would be limited by the use of standard procedures and personal protective equipment (PPE).

Dermal, ocular and inhalation exposure to the notified chemical (≤ 0.5%) may occur during spray application of the finished paints to automobile parts and when cleaning spray gun equipment. The notifier states that these processes will be carried out in a dedicated spray booth with downdraft ventilation, with the use of PPE including an air-fed respirator, which would substantially reduce exposure.

Workers may also contact the dried paint surfaces, however in this form the notified chemical is expected to be incorporated in the paint matrix, and to not be bioavailable.

6.1.2. Public Exposure

Products containing the notified chemical will not be sold to the general public. Automotive refinish paints will only be used by professional automotive repairers. The public may come into contact with auto body parts and automobiles after the paints have been applied and dried however the notified chemical (≤ 0.5% concentration) will be incorporated within the paint matrix and is not expected to be bioavailable.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical and a chemical that is structurally similar to the notified chemical are summarised in the table below. The results of new toxicological investigations conducted on the notified chemical are asterisked, with full details in Appendix A.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
*Rat, repeat dose oral toxicity – 28 days.	NOAEL = 1000 mg/kg bw/day

*Mutagenicity – bacterial reverse mutation	non mutagenic
*Genotoxicity – *in vitro* chromosome aberrations in Chinese hamster V79 cells	non genotoxic
*Genotoxicity – *in vitro* chromosome aberrations in cultured human peripheral blood lymphocytes	non genotoxic
*Genotoxicity – *in vivo* mouse bone marrow micronuclei test	non genotoxic
*Genotoxicity – *in vivo* unscheduled DNA synthesis	non genotoxic

Toxicokinetics, metabolism and distribution.
No information is available on the toxicokinetics of the notified chemical. The notified chemical has a low molecular weight (< 500 Da) but of low water solubility (1.0×10^{-4} g/L) therefore dermal absorption is limited. The respirable fraction is significant (24-33%) and most of the particles can be inhaled (~95%) allowing for accumulation in the respiratory tract and transport to the gastrointestinal tract, however the notified chemical is not introduced in powder form.

Acute toxicity.
The notified chemical was of low acute oral (LD50 > 2000 mg/kg bw) and dermal (LD50 > 2000 mg/kg bw) toxicity in the rat with no deaths or body weight effects noted in either study. Effects reported in the oral study included dyspnea (for up to 5 hours after administration), hunched posture (for up to one day) and piloerection (for up to 2 days after dosing). Effects reported in the dermal study included slight piloerection and slight erythema (which could be attributed to dark red colour of the test substance) in all animals on day 1.

Both toxicity studies were carried out in accordance with OECD Guidelines (OECD TG 401 and 402).

Irritation and sensitisation.
The notified chemical was non-irritating to the rabbit skin and slightly irritating to the rabbit eye. Effects on the conjunctiva were observed up to 48 hours.

The notified chemical was non-sensitising in the guinea pig adjuvant test (using 30% w/w for induction and 10% w/w for challenge).

All of the studies were carried out in accordance with OECD Guidelines (OECD TG 404, 405 and 406).

Repeated dose toxicity.
In a 28-day repeated dose oral toxicity study in the rat, the No Observed (Adverse) Effect Level (NOAEL) was established by the study authors as 1000 mg/kg bw/day, the highest dose tested. The level of significance of some changes in behaviour, clinical chemistry and haematology were however not clear.

Mutagenicity/Genotoxicity.
The notified chemical was non-mutagenic in a bacterial reverse mutation assay. It was also non-genotoxic in two *in vitro* chromosome aberration studies (using Chinese hamster V79 cells and cultured human peripheral lymphocytes) and two *in vivo* studies (mouse bone marrow micronuclei test and unscheduled DNA synthesis in rat peripheral hepatocytes).

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Dermal, ocular and inhalation exposure to workers may occur during end-use of products containing up to 0.5% of the notified chemical. However, based on available information, the notified chemical is of low toxicity.

No inhalation toxicity study was provided and most of the particles are inhalable, however the chemical is not introduced in powder form. The notified chemical's low concentration in end-use products, including those which will be used in spray painting, lessens the concern for inhalation exposure. Furthermore, the use of PPE

and of local exhaust ventilation during spray application will further reduce exposure to workers. Based on available information, the risk to workers is not considered to be unreasonable.

6.3.2. Public Health

Products containing the notified chemical will not be sold to the general public. The notified chemical will not be bioavailable from contact with painted auto body parts and automobiles since it will be incorporated within the paint matrix. Based on negligible exposure, the risk to the public is not considered to be unreasonable.

ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia. Therefore, there will be no release from this activity. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemical is expected to be collected with an inert absorbent material and disposed of in accordance with local regulations, which is most likely landfill.

RELEASE OF CHEMICAL FROM USE

Paint products containing the notified chemical are only available to industrial users, i.e. automotive repairers. Any losses from overspray (estimated at 30% of annual import volume) during industrial use are expected to be collected using standard engineering controls such as spray booths. These losses, together with residues in application equipment washings and empty paint containers (estimated to be up to 5% and 2.5% of the annual import volume, respectively) are expected to be disposed of in accordance with local regulations, which is most likely landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical in paints is expected to share the fate of the metal substrates to which it will be applied. It may be either thermally decomposed during metal reclamation processes or disposed of to landfill at the end of the useful life of the associated articles. Any wastes from spills, equipment washing and empty containers are expected to be disposed of in accordance with local regulations, which is most likely landfill.

7.1.2. Environmental Fate

Based on the provided fate studies, the notified chemical is not readily biodegradable. It is also not bioaccumulative. For the details of the environmental fate studies please refer to the summaries below.

The majority of the notified chemical is expected to share the fate of metal substrates to which it has been applied. The notified chemical is likely to be either thermally decomposed during metal reclamation processes or disposed of to landfill at the end of the useful life of the article to which it has been applied. A small proportion of the notified chemical may be sent to landfill as wastes generated from application. No significant release to the water environment is expected based on the proposed use pattern. In landfill, the notified chemical will undergo natural abiotic or biotic degradation processes. With thermal decomposition or natural degradation in the environment, the notified chemical is expected to finally form water and oxides of carbon, nitrogen and sulphur.

Environmental fate study summaries

Ready biodegradability
The ready biodegradability of the test substance was determined following OECD TG 301B by exposing to activated sludge for measurement of the accumulated quantities of carbon dioxide. Good laboratory practice (GLP) principles were also followed. The test substance is considered structurally similar to the notified chemical. The test levels were 10.5 mg/L and 21.3 mg/L.

No degradation of the test substance was detected by day 28. No toxicity control was performed. However, a separate study for sludge bacteria toxicity showed that the test substance was not inhibitory to sludge micro-organisms. Therefore, the test substance and, by inference, the notified chemical are considered to be not readily biodegradable based on the test outcome (CIBA-GEIGY, 1992b).

Bioconcentration

The bioconcentration study was performed with carp following a Japanese test guideline, the Test on the Degree of Bioconcentration in Fish and Shellfish, which was referenced to OECD TG 305. Good laboratory practice (GLP) principles were also followed. Two concentrations were selected: 0.5 mg/L as a high exposure level and 0.05 mg/L as a low exposure level. The carps were kept in the aquarium where the notified chemical was introduced continuously to maintain constant concentrations. An adequate amount of methanol was used in the preparation of the stock solution and was volatilized before the test. Dispersant (Tween 80) was also used in the test. A blank control with the dispersant was performed.

The notified chemical was a mixture consisting of various components. In the test results, 13 components were detected by High Performance Liquid Chromatography (HPLC). As the results of the 28 days up taking stage, the bioconcentration factors (BCFs) of all components for the steady stage were less than 50 both at the high and low exposure levels. The depuration test was not conducted. The notified chemical is not considered to be bioaccumulative based on the test outcome (Institute of Ecotoxicology, 2005).

7.1.3. Predicted Environmental Concentration (PEC)

The Predicted Environmental Concentration (PEC) has not been calculated since no significant release of the notified chemical to the aquatic environment is expected based on the proposed use pattern.

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 the following study summaries.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 > 100 mg/L	Not harmful to fish
Daphnia Toxicity	48 h EC50 > 100 mg/L	Not harmful to *Daphnia*
Algal Toxicity	72 h EC50 > 100 mg/L 72 h NOEC = 100 mg/L	Not harmful to alga
Inhibition of Bacterial Respiration	3 h EC50 > 100 mg/L	Not inhibitory to bacteria respiration

The notified chemical is not considered harmful up to the limit of the water solubility to aquatic species based on the above acute endpoints. Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is not harmful to aquatic organisms and is not formally classified. On the basis of the acute toxicity and the lack of ready biodegradability, the notified chemical is also not classified under GHS for chronic effects.

Ecotoxicity study summaries

Zebra Fish

The acute toxicity of the notified chemical to zebra fish (*Brachydanio rerio*) was determined in a 96-hour static test according to the OECD TG 203. Good laboratory practice (GLP) principles were also followed. A limit test was performed using filtered (0.45 µm pore size) water accommodated fractions (WAFs) of the test item at a loading rate of 100 mg/L. The test item concentration in the test medium was determined using HPLC to be in the range of 0.97 to 1.3 µg/L during the test period of 96 hours.

All test guideline validity criteria were met. No mortality or other visible abnormalities were observed throughout the test in the control and the test vessels. The 96 h LL50 was determined to be > 100 mg/L, and the 96 h NOEC was determined to be 100 mg/L.

The notified chemical is not harmful to zebra fish up to its solubility under the present test conditions (RCC, 2008b).

Daphnia magna

The acute toxicity of the notified chemical to *Daphnia magna* was determined in a 48-hour static test according to the OECD TG 203. Good laboratory practice (GLP) principles were also followed. A limit test was performed using filtered (0.45 µm pore size) water accommodated fractions (WAFs) of the test item at a loading rate of 100 mg/L. The test item concentration in the test medium was determined using HPLC to be in the range of 0.15 to 0.17 µg/L during the test period of 48 hours.

All test guideline validity criteria were met. No immobilisation was observed throughout the test in the control and the test vessels. The 48 h EL50 was determined to be > 100 mg/L, and the 48 h NOEC was determined to be 100 mg/L.

The notified chemical is not harmful to *Daphnia magna* up to its solubility under the present test conditions (RCC, 2008c).

Green alga

The influence of the notified chemical on the growth of the freshwater green algal species *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) was investigated in a 72-hour static test according to the OECD Guideline 201.

WAFs with the following loading rates of the test item were tested: 1.0, 3.2, 10, 32, and 100 mg/L. A control was run in parallel. The dispersions were stirred for 3 hours in order to dissolve maximum amounts of the different compounds of the test item in the test water. After the stirring period, the dispersions were filtered through membrane filters. The undiluted filtrates of the dispersions were tested as WAFs. The WAF with the lowest loading rate of 1.0 mg/L was prepared by dilution of the WAF with the loading rate of 3.2 mg/L due to technical reasons.

All test guideline validity criteria were met. The measured test item concentration was determined using HPLC to be was 7.8 and 2.3 µg/L (loading rate of 100 mg/L) at the start and at the end of the test duration, respectively. The 72 h E_rL50 and E_bL50 were determined to be > 100 mg/L, and the 72 h NOEC was determined to be 100 mg/L.

In conclusion, the notified chemical is not harmful to *Pseudokirchneriella subcapitata* up to its water solubility limit under the present test conditions (RCC, 2008d).

Activated sludge

The inhibitory effect of the notified chemical on aerobic waste water bacteria of activated sludge was investigated in a respiration test following OECD TG 209. Good laboratory practice (GLP) principles were also followed. This study examined five nominal test concentrations in the range from 10 mg/l to 100 mg/L. The test showed no inhibition of the respiration rate (-3.1 % to -13.8 %) at concentrations ranging from 10 mg/L to 100 mg/L.

All test guideline validity criteria were met. The 30 minutes EC50 was determined to be > 100 mg/L, and the 30 minutes NOEC was determined to be 100 mg/L.

The notified chemical is not considered inhibitory to sludge bacteria respiration (RCC, 1995).

7.2.1. Predicted No-Effect Concentration

It is not considered necessary to calculate the Predicted No-Effect Concentration (PNEC) since the notified chemical is not considered to be harmful to aquatic species up to the limit of the water solubility.

7.3. Environmental Risk Assessment

The risk quotient (Q = PEC/PNEC) was not calculated since both PEC and PNEC were not calculated. The notified chemical is not expected to pose an unacceptable risk to the aquatic environment based on the low effects and limited release to the environment expected from the proposed use pattern.

On the basis of the assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Surface Tension 62.2-64.4 mN/m at 20 °C

Method	EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks	Concentration: 10 mg/L
Test Facility	CIBA-GEIGY (1992a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat, HanRcc: WIST(SPF)
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days (5F/5M at 0 and 1000 mg/kg bw/d
Vehicle	None
Remarks – Method	Dosage was determined in a range finding study previously conducted on Wistar rats which did not show significant toxicity. All food samples except one met the nominal concentrations for dosage.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5F/5M	0	0
low dose	5F/5M	50	0
mid dose	5F/5M	200	0
high dose	5F/5M	1000	0
control recovery	5F/5M	0	0
high dose recovery	5F/5M	1000	0

No treatment related effects on absolute and relative food consumption were noted at any dose level. The slight increase in absolute and relative food consumption observed throughout the treatment period in males in the mid dose group ($p < 0.05$) occurred during both acclimatisation (days 4 to 8) and treatment (days 15 to 22) periods.

No treatment related effects on body weights and body weight gains noted at any dose level. Statistically significant increase in relative body weights was noted in males at the high dose at day 22 of treatment. Statistically significant increase in both absolute and relative body weights was noted in males at the mid dose at day 22 of treatment.

Clinical Observations

No treatment related effects were observed during daily general clinical observations. One male in the high dose group and one male in the control group showed transient scabs on the nose. There is a discrepancy in the reporting of the following: the study summary mentioned that one female in the high dose group showed hair loss on the left shoulder and another female showed transient scabs on the left shoulder during treatment. However the summary and individual tables showed that both females belonged in the control group.

Behavioural Observations

No treatment related signs were observed during weekly performed detailed behavioural observations. One male treated at high dose displayed no iridic reflex at both eyes at week one; this was not observed during the subsequent weeks and was considered incidental.

Functional Observational Battery

A statistically significant decrease in hind limb grip strength was observed in males at high dose, but was considered by the study authors to be incidental as it did not occur in females.

Male and female animals in the high dose group showed statistically significant increases in mean locomotor activity [males during 0-10 and 10-20 minutes ($p < 0.01$) and females during 0-10 minutes ($p<0.05$)]. The study authors did not consider these findings as adverse since no clinical signs indicative of neurotoxicity were noted during detailed behavioural observations.

Laboratory Findings

No treatment related changes were observed in the haematology parameters. At week 4 of treatment, low dose females showed statistically significant changes in the following: relative neutrophils (increased), relative lymphocytes (decreased) and mean corpuscular volume (decreased). No dose relationship was observed.

Animals treated at the high dose showed statistically significant decreases in the following: relative M-reticulocytes (males), haematocrit (females) and relative basophils (females) however these values were within the ranges of historical reference data.

Statistically significant changes in clinical chemistry were noted in treated animals after four weeks of treatment which were not observed however during the recovery period (in high dose animals):

Treatment	Males	Females
High dose	↑sodium, ↑albumin, ↑protein	↑sodium, ↑albumin, ↑protein, ↑calcium, ↑cholesterol, ↓phosphorus
Mid dose		↑sodium
Low dose	↑albumin	↓phosphorus

After the recovery period (for high dose animals only) a statistically significant decrease in cholesterol level was noted in males and in sodium level in females. The effects seen in the mid and high dose animals above were deemed treatment related, however as they were not seen in the recovery animals they were considered reversible and not adverse.

The effects seen in low dose animals did not follow a dose response relationship as they were not observed in mid dose animals.

Effects in Organs

Statistically significant findings in organ weights noted after the treatment period included the following:

Treatment	Males	Females
High dose		↓ovary to body weight ratio
Mid dose	↓brain to body weight ratio, ↑liver to brain weight ratio	↓absolute kidney weight ↓kidney to body weight ratio
Low dose		↓kidney to body weight ratio

After the recovery period a statistically significant increase in thyroid to body weight ratio was noted in females at the high dose. As there were no accompanying microscopic findings or a clear dose response relationship the effects on organ weights were not considered by the study authors to be treatment related.

There were no statistically significant, dose related macroscopic findings, though sporadic effects were noted from all treatment groups including the control group after four weeks of treatment.

Incidental microscopic findings were also noted which were considered common in laboratory rats of this strain and age and therefore not deemed to be treatment related. For example, kidney tubular vacuolation was noted in both control (5/5 males and 4/5 females) and high dose (5/5 males and 4/5 females) groups but not in the low and mid dose groups.

Remarks – Results

The study authors established a No Observed (Adverse) Effect Level (NO(A)EL) of 1000 mg/kg bw/day for the notified chemical.

Although changes in behavioural observation, clinical chemistry and haematology were observed at this dose, these findings were not considered adverse.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, based on no treatment related adverse effects seen at the high dose.

TEST FACILITY RCC (2008a)

B.2. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbital/βnaphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 1, 5, 10, 50, 100 µg/plate (main test); 3.125, 6.25, 12.5, 25, 50 µg/plate (repeat test) b) Without metabolic activation: 1, 5, 10, 50, 100 µg/plate (main test); 3.125, 6.25, 12.5, 25, 50 µg/plate (repeat test)
Vehicle	Deionised water
Remarks - Method	Dosage was chosen on the basis of a preliminary test, in which precipitation was noted at concentrations > 10 µg/plate. The repeat study was to confirm the results of the main study therefore different concentrations of S9 protein were used - 2 mg/mL (main study) and 4 mg/mL (repeat study).

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	>100	≥50	Negative
Test 2	-	>50	≥25	Negative
Present				
Test 1	-	>100	≥50	Negative
Test 2	-	>50	≥25	Negative

Remarks - Results	The positive controls gave satisfactory responses, confirming the validity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	GenPharmTox (2004)

B.3. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Chinese Hamster
Cell Type/Cell Line	V79 Cells
Metabolic Activation System	S9 fraction from phenobarbital/βnaphthoflavone induced rat liver
Vehicle	Deionised water
Remarks - Method	The concentrations used in the main tests were chosen on the basis of the pre-test, and were limited by precipitation. In general, cytotoxicity occurred at higher concentrations than precipitation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Pre-test 1	39.1, 78.1, 156.3, 312.5, 625, 1250, 2500, 5000	4	4
Test 1	2.4*,4.9*, 9.8*, 19.5, 39.1, 78.1	4	18
Test 2	2.4, 4.9*, 9.8*, 19.5, 39.1, 78.1, 156.3*, 312.5, 625, 1250, 2500, 5000	18	18
Test 2	2.4*, 4.9*, 9.8, 19.5, 39.1, 78.1, 156.3*, 312.5*, 625, 1250, 2500, 5000	28	28
Present			
Pre-test 1	39.1, 78.1, 156.3, 312.5, 625, 1250, 2500, 5000	4	4
Pre-test 2	39.1, 78.1, 156.3, 312.5, 625, 1250, 2500, 5000	24	24
Test 1	9.8*, 19.5*, 39.1*, 78.1, 156.3, 312.5, 625, 1250, 2500, 5000	4	18
Test 2	1.2*, 2.4*, 4.9*, 9.8, 19.5, 39.1	4	28

*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				
Pre-test 1	>5000		≥39.1	Negative
Test 1		>78.1	≥4.9	Negative
Test 2		>2500	≥9.8	Negative
Test 2		>5000	≥4.9	Negative
Present				
Pre-test 1	≥2500		≥78.1	Negative
Pre-test 2	≥2500		≥39.1	Negative
Test 1		≥625	≥19.5	Negative
Test 2		Equivocal (≥9.8 or ≥64.6)	≥2.4	Negative

Remarks - Results: No increase in structural aberrations or polyploidy metaphases was seen. The positive controls produced significant increases in aberrations, confirming the validity of the test system. The increases were not statistically significant and were not considered biologically relevant.

CONCLUSION: The notified chemical was not clastogenic to Chinese hamster V79 vells treated in vitro under the conditions of the test.

TEST FACILITY: RCC-CCR (2007)

B.4. Genotoxicity – in vitro

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
- Species/Strain: Human
- Cell Type/Cell Line: Cultured human peripheral blood lymphocytes
- Metabolic Activation System: S9 fraction from Aroclor induced rat liver
- Vehicle: Ethanol

Remarks - Method: The concentrations tested were limited by low solubility and precipitation. However, except for Test 2 with metabolic activation, mitotic indices were reduced by 50% at the highest tested. There were no protocol deviations expected to have an impact on the study.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	3.39, 4.84, 6.92, 9.89, 14.1, 20.2*, 28.8, 41.2*, 58.8*, 84*, 120, 172, 425, 350, 500	3	22
Test 2	1.25, 2.5, 5, 7.5, 10, 15, 20*, 25*, 37.5*, 50, 75*	22	22
Present			
Test 1	3.39*, 4.84, 6.92*, 9.89, 14.1*, 20.2*, 28.8, 41.2, 58.8, 84, 120, 172, 425, 350, 500	3	22
Test 2	5, 7.5, 10, 15, 20*, 25*, 37.5*, 50, 75*	3	22

*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 (initial)	-	>84	≥14.1	Negative
Test 2 (confirmatory)	-	>75	≥37.5	Negative
Present				
Test 1 (initial)	-	>20.2	≥14.1	Negative
Test 2 (confirmatory)	-	>75	≥50	Negative

Remarks - Results: The positive controls gave satisfactory responses, confirming the validity of the test system.

CONCLUSION: The notified chemical was not clastogenic to human peripheral blood lymphocytes treated *in vitro* under the conditions of the test.

TEST FACILITY: Covance (2003a)

B.5. 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: Mouse/NMRI
Route of Administration: Oral – gavage
Vehicle: Polyethylene glycol 400
Remarks - Method: Five out of six animals per sex were analysed. There were no protocol deviations.
A pre-experiment confirmed that 2000 mg/kg bw was suitable as the highest dose. The positive control, cyclophosphamide, was administered at 30 mg/kg bw.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5F/5M	0	24
II (low dose)	F/5M	200	24
III (mid dose)	5F/5M	600	24
IV (high dose)	5F/5M	2000	24
IV (high dose)	5F/5M	2000	48
V (positive control, CP)	5F/5M	30	24

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity: In the pre-experiment, the following toxic reactions were noted at the

	single oral dose administered (2000 mg/kg bw). Reduction of spontaneous activity was observed in all animals (2F/2M) up to 6 hours post-treatment and in half the animals (1F/1M) up to 48 hours post-treatment. Eyelid closure and apathy were observed in one male at 1 hour post-treatment.
Genotoxic Effects	The mean number of polychromatic erythrocytes with micronuclei (PCEs) was not increased after treatment with the test substance as compared to the mean values of the negative controls.
Remarks - Results	The positive control showed a distinct increase of induced micronucleus frequency. The negative control (vehicle) was comparable with historical data, confirming the validity of the test system. As there was no change in the NCE/PCE ratio after treatment, it is not possible to confirm that the test substance reached the bone marrow. However the presence of clinical signs in treated animals suggests that there was systemic exposure to the chemical.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this *in vivo* bone marrow micronuclei test.
TEST FACILITY	RCC-CCR (1995)

B.6. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo.
Species/Strain	Rat/Fischer 344
Route of Administration	Oral – gavage
Vehicle	Polyethylene glycol 400
Remarks - Method	A range finding study (at 250, 500, 1000, 1500 and 2000 mg/kg bw) was conducted using both male and female rats to determine toxicity levels. Since both sexes behaved similarly in the range finding study, only male rats were used in the main study.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	4M	0	2-4 and 14-16
II (low dose)	8M	500	2-4 and 14-16
III (mid dose)	8M	1000	2-4 and 14-16
IV (high dose)	8M	2000	2-4 and 14-16
V (positive control, DMN)	8M	10 (2-4h), 15 (14-16h)	2-4 and 14-16

DMN = N-dimethylnitrosamine

RESULTS	
Doses Producing Toxicity	There were no toxic effects observed in the range finding and main studies. Non-toxic effects (soft faeces, and faeces and purple staining of the anal/genital area) were observed in male and female animals at 250 mg/kg bw group of the range finding study. In the main study, all treated animals had anal purple stains and animals treated at the mid and high doses had purple stains on the tail and some had soft purple faeces. Discoloured (purple) was noted only in the range finding study, in one animal.
Genotoxic Effects	None of the treated groups yielded a positive mean net nuclear grain count for both 2-4 hr and 14-16 hr post treatment.
Remarks - Results	The positive controls behaved as expected, confirming the validity of the test system. No evidence of unscheduled DNA synthesis was observed in treated animals sacrificed after 2-4 hr and 14-16 hr after treatment.

CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo rat primary hepatocytes.
TEST FACILITY	Covance (2003b)

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