Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

AICIS Evaluation report ER1

Evaluation

Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1''-triester with boric acid (H3BO3)

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Preface

The Australian Industrial Chemicals Introduction Scheme (AICIS) has evaluated Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1''-triester with boric acid (H3BO3) under Part 4 of the Industrial Chemicals Act 2019 (IC Act), in accordance with the Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019 (Transitional Rules). This evaluation report is published in accordance with section 67 of the Transitional Rules.

A secondary notification for this chemical was called by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) in February 2020 under the old law, the Industrial Chemicals (Notification and Assessment) Act 1989 (the Act).

Under section 60 of the Transitional Rules, secondary notification assessments started under the old law and not finalised by 1 July 2020, become evaluations (IC Act).

The Australian Government Department of Health and the Australian Government Department of Agriculture, Water and the Environment staff carry out these evaluations.

You can view and download the report on the AICIS website. You can also request a free copy by contacting AICIS.

Requests and enquiries

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Background

Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1"-triester with boric acid (H_3BO_3) (CAS RN 30989-05-0) was assessed under a standard notification category by the NICNAS in 2013 and 2014. The notified chemical was listed on the Australian Inventory of Chemical Substances (the Inventory) in 2016 following an early listing application.

The chemical was assessed for use as a component of finished brake fluid products for the after-care market under both assessments. Based on the data available at that time, it was not classified as hazardous to human health or to the environment.

NICNAS was notified in 2019 of the availability of a new developmental toxicity study that was not available at the time of the assessments as a new chemical. Based on the developmental toxicity study, the notified chemical may be classified as a hazardous substance.

This evaluation reassesses the human health hazard and risks posed to workers and the public, from the chemical, based on this new information.

Exempt information (Section 75 of the Act)

One applicant has claimed as exempt from publication the following details and data items:

- use details
- import volume

Importation/manufacturing volume and uses

The notified chemical is not manufactured in Australia and is imported as a component of finished brake fluid at < 90% concentration. Repackaging of the finished products into smaller containers for the after-care market (vehicle service stations or the general public) will also take place.

The maximum import volume of the chemical for the secondary notification is up to 200 tonnes per annum compared to the annual introduction volume of up to 1300 tonnes per annum assessed in the original new chemical assessments.

Human health effects

A toxicological study on the chemical for developmental toxicity was submitted for the secondary notification.

- In the study (BASF SE, 2018), mated female New Zealand White rabbits (25/dose) were administered the chemical by gavage (0, 100, 250 or 500 mg/kg bw/day) on gestation days 6 to 28. No test substance-related adverse effects on dams, gestational parameters or foetuses were noted in the animals given 100 and 250 mg/kg bw/day. However, the high-dose level of 500 mg/kg bw/day caused evidence of maternal toxicity, such as abortions/mortality and reduced food consumption. Increased incidences of foetuses showing visceral (urogenital tract) or skeletal (axial skeleton) malformations; external, skeletal and cartilage variations; and total malformations and variations were

also noted in the high-dose group (500 mg/kg bw/day).

A NOAEL (no observed adverse effect level) for maternal toxicity was established as 250 mg/kg bw/day. Since there was evidence for treatment-related adverse effects of the test substance on foetal morphology at the high-dose of 500 mg/kg bw/day, the NOAEL for prenatal developmental toxicity was 250 mg/kg bw/day. These effects were not considered to be secondary to maternal toxicity.

Based on the data submitted at the time of the new chemical assessments, the chemical is of low acute oral and dermal toxicity, non-irritating to the skin, a slight eye irritant and not a skin sensitiser. The chemical was not mutagenic or genotoxic and in a repeated dose toxicity test, minimal effects were observed only at the highest dose of 1000 mg/kg bw/day. No treatment-related effects were seen in foetuses in a rat developmental toxicity study at the highest dose of 1000 mg/kg bw/day. The chemical was not classified as hazardous to human health under the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS, United Nations, 2009) or the Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) following the assessments as a new chemical.

Occupational exposure and health risks

The critical health effect of the chemical is developmental toxicity (foetal development) following repeated exposure.

The main route of exposure to the chemical (at less than 90% concentration) for all workers is dermal while accidental ocular exposure is also possible.

For transport and storage workers, exposure is possible during the event of accidental rupture of containers, but the likelihood of such an event is expected to be low. Therefore, the risk to these workers is expected to be low as repeated exposure to the chemical is unlikely. During repackaging, the risk is also expected to be low due to the use of automated transfer systems and good work practices in place (including the use of PPE) and there are limited activities where worker handling is required.

Workers in automotive service centres could be exposed to the chemical when handling products containing the notified chemical during servicing of brake and clutch systems. However, the increasing use of automated bleeding and refilling units is likely to minimise exposure. This category of workers are most at risk due to the possibility of regular dermal exposure and the hazardous nature of the chemical (developmental effects). This is especially the case for pregnant workers or females of reproductive age. Therefore, the chemical could pose an unreasonable risk to these workers unless adequate control measures to minimise dermal exposure to the chemical are implemented.

The developmental toxicity risk associated with the use of the notified chemical in brake fluids can be mitigated by appropriate classification and labelling to ensure that a person conducting a business or undertaking at a workplace (such as an employer) has adequate information to undertake a risk assessment and determine appropriate controls. This can be further strengthened by the inclusion of directions for use to warn against dermal contact. Provided that adequate workplace controls are also in place to reduce exposure to products containing the notified chemical, the risk to workers is not considered unreasonable.

Public exposure and health risks

Public exposure to the notified chemical (at less than 90% concentration) is expected to be restricted to persons maintaining their own vehicles (DIY brake fluid users). The most common exposure scenario here is expected to be short duration dermal contact with drips and spills while topping up hydraulic fluids and servicing of hydraulic parts.

The risk to the public is considered to be low from use of brake fluid products containing the chemical as users are unlikely to be continuously exposed due to the infrequent nature of ‘do it yourself’ (DIY) brake and hydraulic system servicing and only small volumes of product will be handled. This is despite the the newly identified critical health effect of the chemical (developmental effects) and expected variable use of personal protective equipment (PPE).

Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Environmental effects

Ecotoxicity data were available in the original new chemical assessments. No new ecotoxicological studies were provided for this evaluation. Therefore, the ecotoxicity results, as reported in the new chemical assessments, are reproduced in this evaluation. The chemical is not acutely harmful to fish, aquatic invertebrates, and algae. It is non-inhibitory to microbial respiration. Based on the toxicity to aquatic organisms, the notified chemical is not classified for acute toxicity and long-term hazard for the purpose of regulatory risk assessment.

Environmental exposure and risks

The Risk Quotient (PEC/PNEC) has not been calculated because release of the notified chemical to the aquatic environment is not considered to be significant based on the notified use pattern. The chemical is expected to dissipate quickly via hydrolysis in water. As the chemical is considered to be of low concern to aquatic organisms, based on the assessed use pattern in brake fluid products, the chemical is not considered to pose an unreasonable risk to the aquatic environment.

Recommendations

This section provides the recommendations arising from the evaluation of the chemical, and includes applicable recommendations from the new chemical assessment reports (NICNAS, 2013; 2014). The hazard classification presented below is according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS, United Nations, 2009). Recommendations based on the assessment of new data are marked ND.

Recommendations are directed principally at regulatory bodies and importers.

Implicit in these recommendations is that best practice is implemented to minimise occupational exposure.

Recommendations to regulatory bodies

The chemical is not currently listed in Safe Work Australia's Hazardous Chemical Information System (HCIS).

Based on the evaluation findings, a hazard classification is recommended to Safe Work Australia as below:

- Toxic to Reproduction (Category 2): H361d – Suspected of damaging the unborn child (**ND**)

Advice to industry

Hazard communication

Labels

Importers should update their labels to reflect the updated hazard information in this evaluation. Importers should also review their labels for compliance with 'Labelling of workplace hazardous chemicals – Code of practice' (Safe Work Australia, 2018a).

The following information should be used for products/mixtures containing the chemical, if applicable, based on the concentration of the chemical:

- Concentration ≥ 3%: Suspected of damaging the unborn child (**ND**)

The following precautionary statements are recommended (**ND**):

Prevention:

- P201: Obtain special instructions before use.
- P202: Do not handle until all safety precautions have been read and understood.
- P281: Use personal protective equipment as required OR P280: Wear protective gloves/ protective clothing/eye protection/face protection.*

* Either P281 or P280 can be used until 1 January 2023. After this date, when Australia has transitioned to the 7th revised edition of the GHS (United Nations, 2017), P280 alone is to be used.

Response:

- P308 + P313: IF exposed or concerned: Get medical advice/attention.

Storage:

- P405: Store locked up.

Disposal:

- P501: Dispose of contents/container in accordance with relevant Commonwealth, state, territory and local government legislation.

Only the specific precautionary statements that apply to the hazard classification have been included. According to the GHS principles, a general precautionary statement that may apply in this case is 'P101 - If medical advice is needed, have product container or label at hand'. Although general statements are required for consumer products only, the importers of the notified chemical may choose to include this on workplace labels, particularly where it is likely that the chemical may be available for consumer use.

Safety Data Sheets (SDSs)

Employees must have easy access to SDSs for hazardous substances at their workplace. This is required under the 'Model Work Health and Safety Regulations' (Safe Work Australia, 2016) and the Commonwealth, state and territory regulations. SDSs provide information for anyone using the hazardous substance.

Importers of the notified chemical should:

- update their SDS to show the new hazard identified by this evaluation
- review their SDS for compliance with the 'Preparation of Safety Data Sheets for hazardous chemicals - Code of practice' (Safe Work Australia, 2018b)
- provide employees, who are using the chemical and will likely be exposed to the chemical, easy access to the SDS.

Control measures

Occupational controls

A person conducting a business or undertaking (PCBU) at a workplace should implement the following engineering controls to minimise occupational exposure to the chemical during end-use:

- enclosed, automated processes, where possible
- adequate general and local exhaust ventilation

A PCBU at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the chemical as introduced during end-use:

- avoid contact with skin and eyes

A PCBU at a workplace should ensure that the following PPE is used by workers to minimise occupational exposure to the chemical:

- safety goggles

- protective coveralls
- chemical resistant gloves

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

If products and mixtures containing the chemical are also classified as hazardous to health in accordance with the GHS (United Nations, 2009) as adopted for industrial chemicals in Australia, then PCBUs must adopt workplace practices and control procedures. These must be consistent with provisions of state and territory hazardous substances legislation for handling these products and mixtures.

Disposal

Where reuse or recycling is not appropriate, dispose of the chemical in accordance with relevant Commonwealth, state, territory and local government legislation.

Storage

Users of the chemical should securely close containers and store them according to container label instructions.

Emergency procedures

Users should capture any spills or overflow on-site. They should handle spills or accidental release of the chemical by physical containment, collection and subsequent safe disposal. They should implement local work methods on-site that provide guidance on the appropriate course of action to be taken in the event of spill and ensure the protection of persons and the environment. They must report any spill in accordance with standard Health, Safety and Environment (HSE) incident reporting/recording.

Regulatory obligations

Specific requirements to provide information

This risk assessment is based on the information available at the time of the assessment. The Executive Director may initiate an evaluation of the chemical in certain circumstances. Under section 101 of the IC Act, an introducer (importer/manufacturer) of the chemical has post-assessment regulatory obligations to provide information to AICIS when any of these circumstances change.

This evaluation supports the obligatory conditions specified in the new chemical assessment reports (NICNAS, 2013; 2014). Therefore, the Executive Director of AICIS must be notified in writing within 28 days by the applicants, other importer or manufacturer if any of the following conditions stipulated in the new chemical assessment reports arise:

- the function or use of the chemical has changed from a component of finished brake fluid products
- the amount of chemical being introduced has increased, or is likely to increase, significantly
- the chemical has begun to be manufactured in Australia
- information becomes available on the hazards to human health or the environment from the use of the chemical that is not identified in this report
- information becomes available that indicates an increase in the severity of the hazards of the chemical identified in this report

The occupational exposure and occupational health risk characterisation sections (4.1.2 and 6.1 respectively) provide a basis for the conclusion of a potential risk to workers of developmental toxicity associated with a change in the process for handling or repackaging of brake fluids containing the chemical from that described in this evaluation report. The Executive Director of AICIS therefore considers that, in order to manage the risk to worker health, it is necessary to vary the terms of the Inventory listing relating to the industrial chemical to include a requirement that the Executive Director be informed if, when the chemical is introduced as a component of brake fluids, it will be handled or repackaged differently to the way described in this report such that exposure to workers and the public may be increased.

Abbreviations and acronyms

Abbreviation / acronym	Definition
AICIS	Australian Industrial Chemicals Introduction Scheme
Act, the	Commonwealth Industrial Chemicals (Notification and Assessment) Act 1989
bw	body weight
CAS RN	Chemical Abstracts Service Registry Number
Da	Daltons (units of molecular weight)
EC50	median effective concentration or half maximal effective concentration
g	gram gestation day
GHS	Globally Harmonised System of Classification and Labelling of Chemicals (United Nations)
h	Hour
hazard	inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent; intrinsic property of a substance to cause harm
HCIS	Hazardous Chemical Information System
IC Act	Industrial Chemicals Act 2019
IR	infrared
kg	kilogram
kPa	kilopascals
L	litre
LD50	median lethal dose
m^3	cubic metre
ug	microgram
mg	milligram
mg/kg bw	milligram per body weight
min	minute
mL	millilitre
MS	mass spectroscopy
(M)SDS	(Material) Safety Data Sheet, also see SDS
ND	new data
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PCBU	person conducting a business or undertaking
PEC	predicted environmental concentration
Pow	octanol-water partition coefficient
PNEC	predicted no effect concentration
PPE	personal protective equipment
risk	probability or likelihood of harm and the likely extent of the harm; the probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent
SDS	Safety Data Sheet (also see MSDS)
T	tonnes
TG	test guideline
UV	ultraviolet
VIS	visible

1. Introduction

1.1 Background

The chemical, Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1''-triester with boric acid (H3BO3) (CAS RN 30989-05-0) was assessed twice by NICNAS as a new chemical under Section 32 of the Industrial Chemicals (Notification and Assessment) Act 1989 (the Act) under the standard notification category. The new chemical assessment reports were published in 2013 and 2014 and the chemical was listed on the Australian Inventory of Chemical Substances (the Inventory) in December 2016 following an early listing request. No human health or environmental hazard classification was made at the time of the new chemical assessments.

NICNAS was notified in 2019 of a new developmental toxicity study. Based on the new data, the notified chemical may be classified as a hazardous substance. This requires us to reassess the human health hazard and risks of the chemical to workers and the public

This evaluation focuses on the new health hazard data provided.

Data submitted for the original assessment on use and toxicity are summarised in this report in the relevant sections. Details of the studies provided for assessment as a new chemical are reproduced in the appendix. New data submitted for this evaluation are discussed in detail and identified by the abbreviation **ND**.

1.2 Declaration

NICNAS published a notice in the February 2020 Chemical Gazette, requiring a secondary notification of Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1''-triester with boric acid (H3BO3), in accordance with Section 65(2) of the Act. The secondary notification applied to all persons who manufacture and import the chemical and products containing the chemical for use in brake fluid applications. The declaration required the provision of any information relevant to the assessment of the chemical that was not covered in the new chemical assessment and included the following:

Chemical identity, properties and uses

- name(s) of the chemical and of the products containing the chemical under which it is marketed
- annual import and manufacture volumes of the chemical
- concentration of the chemical as imported and in end-use products
- if importers and manufacturers of the chemical are formulating end-use products, the description of the formulation/packing process
- description of the handling of the chemical during transportation, storage, repackaging, reformulation (if any) and use, including:
    - description of work done by each category of workers (transportation, storage, repackaging, reformulation (if any), and end use)
    - for each category of worker handling the product containing the chemical, the number of workers involved in each category, frequency and duration of each activity (e.g. hours per day and days per year)
    - measures in place to prevent worker exposure
    - measures to prevent public exposure.

Human health data

- toxicology data for the chemical, including reproductive and/or developmental toxicity
- information on absorption of the chemical through the skin.

Safety Data Sheet (SDS)

- copies of SDSs for the chemical and products containing the chemical.

1.3 Objectives

The objectives of this evaluation are to review the new data made available since the publication of the new chemical assessment reports and reassess the:

- human health hazards
- risks of adverse effects resulting from exposure to workers and the public from the use of the chemical.

Based on the above, make appropriate recommendations to control exposures and reduce potential risks for workers and public, as required.

1.4 Peer review

During all stages of preparation, this evaluation report has been subject to internal peer review.

1.5 Applicants

Following the secondary notification declaration of Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1"-triester with boric acid (H3BO3), three companies applied for reassessment of this chemical. In accordance with the Transitional Rules, each applicant was provided with a draft copy of the report for comment during the corrections/variations phase of the evaluation.

The applicant details are as follows:

BASF Australia Limited
AC/EAU, Level 12
28 Freshwater Place
Southbank VIC 3006

Clariant (Australia) Pty Ltd
Level 3, Olympus Building, 3 Acacia Place
296-324 Ferntree Gully Road
Notting Hill VIC 3168

HSY Autoparts Pty Ltd
Unit 22, 107-113 Heatherdale Road
Ringwood VIC 3134

1.6 Exempt information

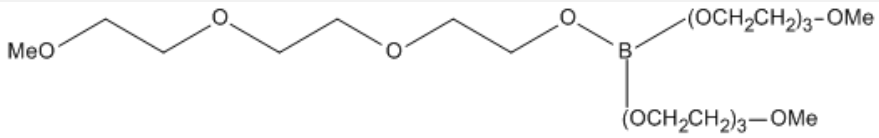
One applicant, Clariant (Australia) Pty Ltd, has claimed the following details as exempt from publication under Section 75 of the Act:

- use details
- import volume

2. Chemical identity, physical and chemical properties

The chemical identity, physical and chemical data assessed by NICNAS in the new chemical assessment report (NICNAS, 2013; 2014) are reproduced in this report without significant modification. Some of this information was treated as exempt information at the time of the original assessment and was not published in the public report. New data submitted for this secondary notification assessment are indicated as ND.

2.1 Chemical identity

Chemical name	Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1"-triester with boric acid (H3BO3)
CAS RN	30989-05-0
Marketing names	Confidential
Other names	Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, triester with boric acid (H_3BO_3), Triethylene glycol monomethyl ether borate (3:1) Triethylene glycol monomethyl ether orthoborate Trimethoxytriglycol orthoborate Tris [2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate Tris {2-[2-(2-methoxyethoxy)ethoxy]ethyl} borate (IUPAC) B-TEGME Borated Tri-Ethylene Glycol Methyl Ether
Molecular formula	$C_{21}H_{45}BO_{12}$
Structural formula	
Molecular weight	500.4 Da
Spectral data	Reference MS, IR, NMR and UV-VIS spectra were provided

2.2 Composition

Degree of purity: 85-99%

Non-hazardous impurities/residual monomers (> 1% by weight)

Chemical name	Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-		
CAS no.	112-35-6	Weight %	7-13
Chemical name	Ethanol, 2-methoxy-, manuf. of, by-products from, esters with boric acid (H_3BO_3)		
CAS no.	161907-80-8	Weight %	1-2

Additives/Adjuvants: None

2.3 Physical and chemical properties

The physical and chemical properties for the chemical are shown in Table 2.1. No new data were submitted for the secondary notification assessment.

Table 2.1 – Summary of physical and chemical properties

Property	Value	Data Source/Justification
Appearance at 20ºC and 101.3 kPa	Light-yellow, clear liquid	
Melting/freezing point	< -55°C	Measured (OECD TG 102)
Boiling point	361°C (decomposition)	Measured (OECD TG 103)
Density	1,070 kg/m^3 at 20°C	Measured (92/69/EEC, pycnometer)
Vapour pressure	0.12 kPa at 20°C 0.41 kPa at 50°C	Measured (92.69/EEC, static method)
Water solubility	Not determined	Measurement is not applicable due to spontaneous hydrolysis. Hydrolysis products are highly soluble in water.
Hydrolysis as a function of pH	Spontaneous at pH 1.2, 4.1, 7.1 and 8.9 at ambient temperature	Measured (OECD TG 111)
Partition coefficient (n-octanol/water)	Not determined	Measurement is not applicable due to rapid and complete hydrolysis within minutes.
Adsorption/Desorption	Not determined	Expected not to partition to soil from the water based on predominantly hydrophilic chemical structure; anticipated to undergo rapid and complete hydrolysis.
Dissociation constant	Not determined	Does not contain dissociable functionalities.
Flash point	146°C at 101.3 kPa	BASF (2010)
Flammability	Not determined	Based on the flash point not classified as flammable
Autoignition temperature	310 ± 5 °C at 101.3 kPa	BASF (2010)
Explosive properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising properties	Not determined	Contains no functional groups that would imply oxidising properties
Explosive properties	Not shock or thermally sensitive	Measured

Comments on physico-chemical properties

Reactivity

The notified chemical is expected to be stable under normal conditions of use. However, it is subject to spontaneous hydrolysis in the presence of water, due to the ester groups, to form triethyleneglycol, diethyleneglycol and boric acid.

3. Importation and use

Importation

The notified chemical is not manufactured in Australia and will be imported by sea as a component of finished brake fluid preparations at less than 90% concentration. The finished products containing the chemical will be imported in small packages (1-30L), in 1000 L intermediate bulk containers (IBCs) or in bulk isotainers (20 tonnes). The products will be transported from the dockside by road to approved chemical warehouses and logistics facilities or directly to end-users' sites. The brake fluid imported in small packs (1-30L) is not repackaged or reformulated however the larger containers (≥ 1,000 L) will be repackaged into smaller pack sizes (0.25-40L). These smaller packs will be distributed via a major petroleum company or wholesaler to retail outlets.

The maximum introduction volume of the chemical over the next five years will be up to 200 tonnes per annum, as compared to an annual introduction of 1300 tonnes per annum originally assessed in 2013 and 2014.

Use

The notified chemical will be imported as a component of finished brake fluid preparations at up to 90% concentration.

4. Exposure

New information on the use of Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-, 1,1',1''-triester with boric acid (H_3BO_3) provided for the evaluation has not altered public or occupational exposure. Therefore, the following sections on public, occupational and environmental exposure have been reproduced from the two new chemical assessment reports (NICNAS, 2013; 2014) without significant modification.

4.1 Occupational exposure

4.1.1 Operational description

The notified chemical will be imported as a component of finished brake fluids at up to 90% concentration. Repackaging of the finished products into smaller containers for the after-care market (vehicle service stations or private individuals) will also take place.

Repackaging

Repackaging from 1,000 L IBCs or bulk containers to smaller containers will be undertaken using dedicated packing lines. This process will be automated and operators will attach and detach suction nozzles that pump the brake fluid directly into the filling line or into header tanks. The product containers, and outer packaging for transporting multiple containers, are labelled with the appropriate GHS hazard statements and pictograms as well as descriptions of the safe work practices and PPE required to minimise exposure to the notified chemical during use.

End-use

While the notified chemical was originally assessed for use in car manufacturing to fill brake fluid reservoirs on new cars, this process has been discontinued.

At vehicle service stations or with private users, brake fluid reservoirs will be topped up manually by pouring from a container. During routine service, brake or clutch repair, fluid in the entire system may be replaced. This will be done manually or, at many vehicle service stations, fluid reservoirs will be refilled using an electronic brake bleeding unit (with electronic pressure control) to remove and replace all of the used brake fluid in the system.

This table summarises the number and category of workers.

Category of worker	Exposure duration (hours/day)	Exposure frequency (days/year)
Packaging operators	2-3	< 10
Service station/private users	1	< 50

4.1.2 Estimates of occupational exposure

Transportation and storage

Transport and storage workers may come into contact with the notified chemical as a

component of finished brake fluids (at < 90% concentration) only in the event of accidental rupture of containers.

Repackaging

Repackaging will be largely automated; however, workers may be exposed (dermal and ocular) to drips and spills of the notified chemical (at less than 90% concentration) when manually connecting and disconnecting suction nozzles that pump the brake fluid either directly into the filling line or into header tanks. Dermal and ocular exposure is mitigated through the stated use by the notifier of PPE including gloves, goggles and protective clothing.

End-use

The most widespread source of occupational exposure to the notified chemical (at less than 90% concentration) will be during servicing of automotive brake systems and other hydraulic parts, both during topping up of hydraulic fluids and during servicing of the lines containing the fluid. The conditions of exposure in automotive service centres will vary, and it is not likely that appropriate PPE will be used in all (or, indeed, most) cases. There may therefore be widespread and regular dermal exposure of workers to drips and spills of the notified chemical. However, the increasing use of automated bleeding and refilling units will likely minimise worker exposure. Secondary ocular exposure, from contact with material on the hands, is also possible; direct ocular exposure may also occur.

4.2 Public exposure

Public exposure to the notified chemical (at less than 90% concentration) is expected to be almost completely restricted to do-it-yourself (DIY) users who conduct automobile maintenance. The more common exposure scenario is expected to be dermal contact with drips and spills while topping up hydraulic fluids, but there may be more extensive dermal and ocular exposure during servicing of hydraulic parts. As for occupational exposure during vehicle servicing, the use of PPE is expected to be variable; however, the frequency of exposure is expected to be much lower for members of the public than for automotive service workers.

4.3 Environmental exposure

4.3.1 Releases

Release of chemical at site

The notified chemical will be imported into Australia as a component of finished brake fluid products at < 90% in containers of up to 20 T in size. Environmental release of the notified chemical during importation, storage and transportation is not expected except in the event of accidental spills or leaks. Spills or leaks of a drum is expected to be collected with inert material and disposed of to landfill.

The brake products in the 1000 L IBCs and 20 T isocontainers will be repackaged in Australia. To contain spills at the repackaging site, bunding is in place in all tank areas, where collection of process spills occurs in onsite collection pits. Spilled material is not expected to be significant and will be either collected by licensed disposal firms or consigned to sewer under licence.

The IBCs and isocontainers when emptied will be cleaned and reused. The residues in the empty containers are estimated to be up to 100kg per annum and are expected to be consigned to sewer from the cleaning process.

Release of chemical from use

During end use, release of the notified chemical contained in the brake fluid may occur mainly through leakages from the hydraulic systems in vehicles, accidental spills during brake fluid changes, and during disposal of used fluids following changes. The notifiers anticipate that users of the brake fluid formulation will include 97% professional after-care and 3% private after-care. The following estimates of releases for each of these usage patterns are:

a) Professional after-care

   Residues in packaging (0.25-30 L), (97% of 100 T) with 0.1% residues = 97 kg/annum

   Spills and leaks, <0.1% of (97% of 100 T) = 97 kg/annum

b) Private after-care

   Residues in small packaging (0.25-1 L), 3% of 100 T with 0.1% residues = 3kg/annum

   Spills and leaks, <0.1% of (3% of 100 T) = 3kg/annum

The combined annual total of waste is approximately 200kg brake fluid formulation, containing up to 180kg notified chemical, which may be released to sewer for the worst case scenario. Car manufacturers recommend draining and refilling of brake fluid systems every two years. It is expected that most brake fluid removed from the reservoirs in vehicles at motor garages will be collected and sent for oil recycling for reuse or for further use of the calorific value. Minimal residues will be disposed of to sewer under licence.

Release of chemical from disposal

Material spilled during repackaging will be either collected by licensed disposal firms or consigned to trade waste sewer under licence, while residues from the cleaning and drum recycling process are consigned to sewer under licence.

Residues of the brake fluid in empty containers in non-industrial locations are expected to be discarded with domestic garbage and disposed of at licensed landfill sites. Used brake fluid remaining after oil changes is likely to be recycled. The SDSs recommend disposal in accordance with government regulations for the disposal of special waste, which may include oil recycling or reuse of the calorific value.

4.3.2 Fate

The notified chemical is expected to be readily biodegradable (BASF, 1999a). For details of the environmental fate study, refer to Appendix B. The notified chemical is also expected to hydrolyse rapidly. Since the components of the brake fluid are hygroscopic, it is likely that water would become absorbed during normal usage of the formulations containing the notified chemical, and consequently it is likely that some of the notified chemical will

hydrolyse to boric acid and neutral organic chemicals to undergo further biodegradation.

A bioaccumulation study was not provided. The notified chemical is not expected to bioaccumulate given its high water solubility and low predicted log P_{OW}.

Most of the notified chemical is expected to be used as a component in the brake fluid, which may be recycled or reused for the calorific value. The associated notified chemical is expected to be either thermally decomposed during the recycling or to be reused for the calorific value as a component of the reused oil. In either case, it is expected to be decomposed into water, oxides of carbon and boron.

A small amount of the chemical may also be sent to landfill as residues in empty containers. In landfill, it may have potential to leach into public water however it hydrolyses rapidly and the products are highly water soluble. In water, the notified chemical is expected to hydrolyse rapidly followed with further degradation.

The notified chemical is expected to be released to sewer as residues from container cleaning and recycling, and spills from repackaging. Given the high water solubility, the chemical is expected to remain in the effluent water of the sewage treatment plants. In water, it is expected to hydrolyse rapidly followed with further degradation. In public water or landfill, the chemical is expected to undergo abiotic and biotic degradation processes, forming water, oxides of carbon and boron.

4.3.3 Predicted environmental concentration (PEC)

Up to 180kg notified chemical may be released to the sewer from residue cleaning and spills, which is not considered to be significant as it will be released to sewer throughout Australia. The chemical is readily biodegradable and hydrolysed rapidly; so it is not persistent in the aquatic environment. It is expected to dissipate quickly via hydrolysis in water. In addition, the chemical is considered to be of low concern to aquatic organisms as shown below in Section 5.2.1. Therefore, the calculation of Predicted Environmental Concentration (PEC) is not considered to be necessary.

5. Hazard assessment

5.1 Physicochemical and human health hazard assessment

This section summarises all the data relevant to the physicochemical and human health hazard assessment of the chemical, with a focus on new data. New data submitted for the evaluation are summarised in this section and designated as **ND**. The robust summary of the new human health study is provided in Appendix A1 of this report.

The robust summaries of the toxicological data available for the assessment of the chemical as a new chemical are reproduced from the new chemical assessment reports (NICNAS, 2013; 2014) in Appendix A2 of this report.

5.1.1 Physicochemical effects assessment

The applicant submitted no new physicochemical data for the evaluation.

5.1.2 Human health effects assessment

The results from toxicological investigations conducted on the chemical are summarised in table 5.1. While the results of the new toxicological investigation are discussed in some detail below, the studies assessed as part of the new chemical assessments are only briefly summarised.

Toxicokinetics

Toxicokinetic studies (absorption, metabolism, distribution, elimination) for the notified chemical are not available. Due to its relatively high molecular weight (> 500 Da) and spontaneous hydrolysis under physiological conditions the potential for dermal absorption of the chemical itself is expected to be limited. All hydrolysis products (triethyleneglycol, diethyleneglycol and boric acid) are highly soluble in water and therefore it can be assumed that observed effects in toxicological studies are likely caused by these products, most likely boric acid. However, it should be noted that dermal absorption of boric acid through intact skin is very low (0.23%) in adult humans (Wester et al., 1998)

Acute toxicity

Acute oral (Hoechst, 1995a) and dermal (BASF, 2010) toxicity studies submitted for the new chemical assessments concluded low toxicity (LD50 > 2,000 mg/kg).

No acute inhalation toxicity data were provided. Inhalation exposure is unlikely based on the low vapour pressure of the notified chemical (0.12 kPa at 20°C).

Skin irritation

A dermal irritation study (Hoechst, 1995b) concluded the chemical was non-irritating to the skin.

Eye irritation

In an eye irritation study (Hoechst, 1995c) in rabbits, the chemical was found to be slightly irritating.

Sensitisation

No evidence of skin sensitisation was observed in two guinea pig maximization tests (BASF, 2010) performed on a brake fluid formulation containing 37% notified chemical. The results of the studies are consistent with the absence of structural alerts for sensitisation for the notified chemical.

Repeated dose toxicity

In a 90-day repeated dose oral toxicity study (Harlan, 2013a) in rats, the NOAEL for the notified chemical was established as 1000 mg/kg bw/day (the highest dose) based on no test-substance-related changes at any of the doses administered.

Mutagenicity/Genotoxicity

The chemical was negative in two bacterial reverse mutation tests (BASF, 1989; Dr. U. Noack-Laboratorien, 2007) and not genotoxic in an in vitro chromosomal aberration study on human peripheral lymphocytes (BASF, 2010).

Reproductive and developmental toxicity

In an oral prenatal developmental toxicity study (Harlan, 2013b) in rats submitted for the new chemical assessments, the NOEL for the notified chemical was established as 1000 mg/kg bw/day, based on the absence of treatment-related effects at any of the doses administered.

In a developmental toxicity study (IUCLID, 2000) conducted with a brake fluid formulation containing the notified chemical (concentration not reported) no test substance related effects were observed in either dams or pups at the maximum dose tested of 1000 mg/kg bw/day.

In a prenatal developmental toxicity study (BASF SE, 2018; **ND**), mated female New Zealand White rabbits (25/dose) were administered the chemical by gavage (0, 100, 250 or 500 mg/kg bw/day) on gestation days 6 to 28. No test substance-related adverse effects on dams, gestational parameters or foetuses were noted in the animals given 100 and 250 mg/kg bw/day. However, the high-dose level of 500 mg/kg bw/day caused evidence of maternal toxicity, such as abortions/mortality and reduced food consumption. Increased incidences of foetuses showing visceral (urogenital tract) or skeletal (axial skeleton) malformations; external, skeletal and cartilage variations; and total malformations and variations were also noted in the high-dose group.

A NOAEL for maternal toxicity was established as 250 mg/kg bw/day. Since there was evidence for treatment-related adverse effects of the test substance on foetal morphology at the high-dose of 500 mg/kg bw/day, the NOAEL for prenatal developmental toxicity was 250 mg/kg bw/day. These effects were not considered to be secondary to maternal toxicity.

Table 5.1 – Summary of toxicological data

Endpoint	Result and assessment conclusion
Rat, acute oral	LD50 > 2,000 mg/kg; low toxicity
Rat, acute dermal	LD50 > 2,000 mg/kg; low toxicity
Rabbit, skin irritation	Non-irritating
Rabbit, eye irritation	Slightly irritating
Guinea pig, skin sensitisation - Maximisation test*	No evidence of sensitisation
Rat, repeat dose oral toxicity - 90 days	NOAEL = 1000 mg/kg bw/day
Genotoxicity - bacterial reverse mutation	Non-mutagenic
Genotoxicity - in vitro chromosomal aberration test	Non-genotoxic
Developmental toxicity – prenatal study in the rat	NOEL = 1000 mg/kg bw/day
Reproductive and developmental toxicity -study in the rat*	NOAEL (maternal/developmental) = 1000 mg/kg bw/day
Developmental toxicity – prenatal study in the rabbit (ND)	NOAEL (maternal/developmental) = 250 mg/kg bw/day; developmental toxicant

* data on brake fluid formulation containing notified chemical (concentration not reported)

5.1.3 Hazard classification

Based on the available information, the chemical is classified as hazardous according to the GHS (United Nations, 2009), as adopted for industrial chemicals in Australia. The hazard classification is presented in Table 5.2.

Table 5.2 – Human health hazard classification (ND)

Hazard classification	Hazard statement
Toxic to Reproduction (Category 2)	H361d - Suspected of damaging the unborn child

5.2 Environmental hazard assessment

This section summarises the data relevant to the environmental hazard assessment of the chemical. No new ecotoxicological data were submitted for the secondary notification. Therefore, the environmental effects assessment, predicted no-effect concentration and hazard classification sections have been reproduced from the new chemical assessment reports (NICNAS, 2013; 2014) without significant modification. The robust summaries of the ecotoxicological data available for the new chemical assessments (NICNAS, 2013; 2014) are reproduced in Appendix B.

5.2.1 Environmental effects assessment

The results from toxicological investigations conducted on the chemical are summarised in Table 5.3 and the text below (BASF, 2010 for fish, daphnia, 72 h algae; IUCLID 2000 for 96 h alga; BASF 1999b for microbial activity)

Table 5.3 – Summary of ecotoxicity data

Endpoint	Result	Assessment conclusion

EC50 = median effective concentration

Based on the ecotoxicological endpoints for the notified chemical, it is not considered to be harmful to aquatic life and is not inhibitory to microbial activity.

5.2.2 Predicted no-effect concentration

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated given no PEC was calculated and the expected low concern of the chemical to aquatic organisms.

5.2.3 Hazard classification

The notified chemical was not classified according to the GHS (United Nations, 2009). Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

6. Risk characterisation

The occupational and public health risks posed by the chemical have been updated to account for the change to the human health hazard as reassessed in this secondary notification.

The exposure of the notified chemical to the environment and ecotoxicological hazards have not changed since the original new chemical assessments. Therefore, the environmental risk assessment section has been reproduced from the original new chemical assessment reports without modification.

6.1 Occupational health risk characterisation

The critical health effect of the chemical is the adverse developmental effects following long-term or repeated exposure. However, this health effect was identified from prenatal developmental toxicity testing in animals and is not relevant for non-pregnant workers.

The main route of exposure to the chemical (at less than 90% concentration) for workers is dermal or ocular; however, the potential for accidental ocular exposure should be infrequent.

The risk to transport and storage workers is expected to be low as exposure is only possible during the event of accidental rupture of containers; repeated exposure to the notified chemical in the imported brake fluid product is unlikely under these circumstances. The risk is also expected to be low during repackaging due to the use of automated transfer systems, the good work practices reported to be in place (including the use of PPE) and limited activities where worker handling is required.

Workers most at risk of developmental effects will be those in automotive service centres when handling products containing the notified chemical that do not use automated measures or PPE during servicing of brake and clutch systems. Because of the possible regular dermal exposure of these workers and the hazardous nature of the notified chemical, there is a concern for pregnant workers although the increasing use of automated bleeding and refilling units is likely to minimise exposure. The chemical could pose an unreasonable risk to these workers unless adequate control measures to minimise dermal exposure to the chemical are implemented.

The developmental toxicity risk associated with the use of the chemical in brake fluids can be mitigated by appropriate classification and labeling to ensure that a person conducting a business or undertaking at a workplace (such as an employer) has adequate information to determine appropriate controls. This can be further strengthened by the inclusion of directions for use to warn against dermal contact. Provided that adequate workplace controls are also in place to reduce exposure to the brake fluids containing the notified chemical, the risk to workers is not considered unreasonable.

6.2 Public health risk characterisation

Public exposure to the notified chemical (at less than 90% concentration) is expected to be restricted to persons who maintain their own vehicles. For these DIY brake fluid users, the most common exposure scenario is expected to be short duration dermal contact with drips and spills while topping up hydraulic fluids and servicing of hydraulic parts. While the use of PPE by the public is expected to be variable, despite the newly identified critical health effect of the chemical, the public is at low risk from use of brake fluid products containing the chemical. The low risk is mainly due to the infrequent nature of DIY brake and hydraulic system servicing in motor vehicles and that members of the public are unlikely to be

continuously exposed.

Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

6.3 Environmental risk characterisation

The Risk Quotient (PEC/PNEC) has not been calculated since no PEC or PNEC was available. The potential for rapid hydrolysis and the ecotoxicity data of the notified chemical indicate that it is unlikely to reach ecotoxicologically significant concentrations in the aquatic system based on its proposed use pattern. The notified chemical is expected to have a low potential for bioaccumulation. Therefore, on the basis of the assessed use pattern in brake fluid products, the notified chemical is not considered to pose an unreasonable risk to the environment.

Appendix A: Toxicological investigations

A1 Data for evaluation

The robust summary of the toxicological study submitted for the Secondary Notification assessment of the chemical are presented here.

A1.6 Developmental toxicity – Prenatal developmental toxicity study (ND)

Test substance	Methyltriglycol-o-borat (CAS: 30989-05-0)
Method	OECD TG 414 Prenatal Development Toxicity Study EC Directive 2004/73/EC, B.31
Species/Strain	New Zealand White rabbits (Crl:KBL(NZW))
Route of administration	Oral – gavage
Treatment period	Day 6 through to day 28 of gestation
Vehicle	No vehicle, pure substance
Remarks – method	No significant protocol deviations.

Results

Group	Number and sex of animals	Dose (mg/kg bw/day)	Mortality
Control	25 female	0	0
Low dose	25 female	100	1
Mid dose	25 female	250	0
High dose	25 female	500	3

Mortality and time to death

One low dose animal died after a gavage error. In the high dose group, one animal was found dead on day of sacrifice (gestation day 29) and two animals aborted and were then sacrificed ahead of schedule (gestation days 28 and 29).

Effects on dams

Death or abortion was observed in three high dose animals before term (gestation days 28 and 29). There was reduced defaecation observed in four control, one low-dose, one mid-dose and six high dose animals with no defaecation for three high-dose animals. The higher incidence of reduced/no defaecation in the high-dose group indicated a relationship to the treatment.

There was no statistical difference in the food consumption of control, low- and mid-dose groups. There was a reduction in food consumption for high-dose animals from gestation days 9 to 15 before a recovery on gestation day 17 and an overall decrease in consumption from gestation days 6 to 28 (↓7%).

The high dose group had statistically significant lower body weights than other groups from gestation days 16 to 21; however, at sacrifice, the absolute body weights adjusted for gravid uterine weight were not statistically significantly between all test groups including controls.

Gravid uterine weights in all groups was not significantly different. There were no test substance-related and/or biologically relevant differences in conception rate, mean number of corpora lutea, implantation sites or the incidence of pre- and post-implantation losses, resorptions and viable foetuses.

Effects on the foetus

External soft tissue and skeletal malformations seen in low- and mid-dose groups were not significantly higher than controls and were not treatment-related. One external variation, paw hyperflexion, was recorded in the high-dose group with an incidence of 4.6% versus controls and above the historical control range.

Although foetal soft tissue malformations (including absent and misplaced kidney, absent ureter, absent adrenals) were not significantly different in incidence between groups, multiple visceral malformations affecting the urogenital tract in the high-dose group (mean 1.5%; historical range 0-0.6%) were above the incidence in historical controls.

Incidences of soft tissue variations (cystic dilatation of the brain, mal-positioned carotid artery branches, short innominate artery, absent lung lobe and dilated renal pelvis) in the test groups were not significantly different from the control nor dose-dependent and, therefore, not considered biologically relevant.

Incidences of skeletal malformations in the high dose group including severely malformed vertebral column and/or ribs, misshapen lumbar vertebrae, thoracic hemivertebrae and severely fused sternebrae (bony plate) were all within their historical control ranges with the exception of the last listed.

While skeletal variations for all groups (97.3% – 100%) were above the control (92.1%) and the historical control range (mean 93.9; range 83.2-100.0%), these appeared to be unrelated to the dose in the majority of the cases. For most individual skeletal variation types, increased incidences (outside the historical range) were only seen in the high-dose group with the findings related to vertebral column, sternum and hind extremities. Although two of the findings, supernumerary thoracic vertebra and supernumerary rib (13th, cartilage present), had higher incidences than the controls in all treated groups, the increase was not statistically significant and near the upper limit of the historical range in the low-dose group. In addition, the increase was not dose-related for the supernumerary rib (13th, cartilage present). Supernumerary thoracic vertebrae and supernumerary ribs are generally regarded as of low to moderate concern as they are variations rather than permanent malformations (ECETOC, 2002) and data from adult rabbits indicate that their presence is without significant effect on the wellbeing of the animals.

Foetal malformations/ variations	Affected foetuses/litter				
	Dose (mg/kg bw/day)				Historical controls
	0	100	250	500	Mean % (range)
External malformations	0	1.2%	0.6%	0	- -
External variation (paw hyperflexion)	0	0	0	4.6%*	- (0-0.9%)
Soft tissue malformation	0	0.6%	0.6%	1.5%	- (0-0.6%)
Soft tissue variations	4.9%	1.8%	3.2%	4.5%	- -
Skeletal malformations	0	1.0%	0	2.2%*	- -
Skeletal variations	92.1%	97.3%*	99.1%**	100.0%**	93.9% (83.2% -100.0%)

*** p ≤ 0.05; ** p ≤ 0.01**

Remarks – Results

In the high-dose group, foetuses from different litters were affected by visceral (multiple malformations of urogenital tract) or skeletal (malformations of axial skeleton) malformations, some of which exceeded their historical control ranges. In addition, there were significantly increased incidences of external, skeletal and cartilage variations, all above the historical control range. While the total of these findings caused the significant increase of overall malformations and variations in the high-dose group, these particular values were still within the historical control range of the test facility. Overall, the range of observed anomalies at the high dose (500 mg/kg bw/day) suggest the beginning of developmental toxicity.

Conclusion

The NOAEL for maternal toxicity was 250 mg/kg bw/day, based on abortions/mortality and reduced food consumption at the high-dose level of 500 mg/kg bw/day. The NOAEL for prenatal developmental toxicity was also 250 mg/kg bw/day, based on evidence for treatment-related adverse effects at the high-dose of 500 mg/kg bw/day.

Test Facility BASF SE (2018)

A2 New chemical assessment

The robust summaries of the toxicological studies submitted for the new chemical assessments of the chemical (NICNAS, 2013; 2014) are presented here.

A2.1 Acute toxicity - oral

Test substance	Notified chemical
Method	OECD TG 401 Acute Oral Toxicity – Limit Test
Species/Strain	Rat/Wistar
Vehicle	None
Remarks – Method	No significant protocol deviations

Results

Group	Number and sex of animals	Dose (mg/kg bw/day)	Mortality
1	5 males/5 females	2000	0/10

LD50	> 2000 mg/kg bw
Signs of toxicity	No signs of toxicity were recorded
Effects in Organs	No effects in organs were reported
Remarks – Results	The notified chemical did not cause either deaths or symptoms of toxicity
CONCLUSION	The chemical is of low toxicity via the oral route
TEST FACILITY	Hoechst (1995a)

A2.2 Irritation – skin

TEST SUBSTANCE	Notified chemical
Method	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive 2004/73/EC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of animals	3

Vehicle	None
Observation period	72 hours
Type of dressing	Semi-occlusive
Remarks – Method	No significant protocol deviations
Remarks – Results	No signs of irritation were observed during the study
CONCLUSION	The notified chemical is non-irritating to the skin
TEST FACILITY	Hoechst (1995b)

A2.3 Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation)
Species/Strain	Rabbit/New Zealand White
Number of animals	3
Observation period	72 hours
Remarks – Method	No significant protocol deviations

RESULTS

Lesion	**Mean Score*** <u>**Animal No.**</u>			**Maximum value**	**Maxiumum duration of any effect**	**Maximum value at end of observation period**
	1	2	2			
Conjunctiva: redness	0.3	1	0.7	2	< 72 h	0
Conjunctiva: chemosis	0	0	0	2	< 24 h	0
Conjunctiva: discharge	0	0	0	2	< 24 h	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

***Calculated on the basis of the scores at 24, 48, and 72 hours for each animal.**

Remarks - Results

Conjunctival redness was observed in all animals that persisted in two animals for at least 48 hours. A clear discharge was also observed in all three animals and had cleared by 24 hours. Obvious swelling was observed one hour after application in one animal. All signs of irritation had cleared by 72 hours.

CONCLUSION	The chemical is slightly irritating to the eye.
TEST FACILITY	Hoechst (1995c)

A2.4 Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents EC Directive 88/302/EEC B.26 Sub-Chronic Oral Toxicity Test: 90-Day Repeated Oral Dose Study using Rodent Species
Species/Strain	Rat/Wistar Han:RccHan:WIST
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days
Dose regimen:	7 days per week
Vehicle	Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-
Remarks – Method	No significant protocol deviations

RESULTS

Group	Number and sex of animals	Dose (mg/kg bw/day)	Mortality
control	10 per sex	0	0
Low dose	10 per sex	10	0
Mid dose	10 per sex	100	0
High dose	10 per sex	1000	0

Mortality and time to death

No test substance related deaths occurred during the study.

Clinical observations

No clinical signs of toxicity were noted in the treated animals.

Laboratory findings – Clinical Chemistry, Haematology, Urinalysis

No toxicologically significant effects were noted in the haematological and blood chemical parameters in the treated animals.

Effects in organs

No toxicologically significant effects were detected in the necropsy, histopathology or organ weights in the treated animals.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on the absence of treatment-related toxicological significant effects at any of the doses administered.

TEST FACILITY Harlan (2013a)

A2.5 Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100
Metabolic Activation System	S9 fraction from Aroclor 1254 rat liver
Concentration Range in Main Test	a) With metabolic activation: 20-5000 µg/plate b) Without metabolic activation: 20-5000 µg/plate
Vehicle	Distilled water
Remarks – Method	A preliminary toxicity test was not conducted. An *E.coli* strain was not included in the 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	-	> 5000	> 5000	negative
Test 2	-	> 5000	> 5000	negative
Present				
Test 1	-	> 5000	> 5000	negative
Test 2	-	> 5000	> 5000	negative

Remarks - Results

The test substance was tested up to the maximum recommended dose level of 5000 µg/plate. No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

All the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

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

TEST FACILITY BASF (1989)

A2.6 Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure and Pre incubation procedure

Species/Strain *S. typhimurium*: TA1535, TA1537, TA98, TA100,
E. coli: WP2uvrA

Metabolic Activation System S9 fraction from phenobarbital/β-naphthoflavone induced rat liver

Concentration Range in Main Test Plate incorporation study:
a) With metabolic activation: 50-5000 µg/plate
b) Without metabolic activation: 50-5000 µg/plate
Pre incubation procedure:
a) With metabolic activation: 230-5000 µg/plate
b) Without metabolic activation: 230-5000 µg/plate

Vehicle: Distilled water

Remarks – Method: The negative control was distilled water and positive controls were ICR 191, 4-nitro-o-phenylen-diamine, nitrofurantoine, sodium azide and 4-nitroquinoline-1-oxide in the absence of S9 mix and 2-aminoanthracene and benzo[a]pyrene in the presence of S9 mix.

RESULTS

Metabolic activation	**Test substance cytotoxicity in main test**	**Concentration (µg/plate) precipitation**	**Resulting in: genotoxic effect**
Absent			
Test 1 (Plate incorporation)	> 5000	> 5000	negative
Test 2 (Pre incubation)	> 5000	> 5000	negative
Present			
Test 1 (Plate incorporation)	> 5000	> 5000	negative
Test 2 (Pre incubation	> 5000	> 5000	negative

Remarks - results

The test substance was tested up to the maximum recommended dose level of 5000 µg/plate. No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

All the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

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

TEST FACILITY: Dr. U. Noack-Laboratorien (2007)

A2.7 Developmental toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 414 Prenatal Developmental Toxicity Study.

Species/Strain Rat/Sprague-Dawley Crl:CD(SD) IGS BR

Route of Administration Oral – gavage

Exposure Information Exposure days: 15 days (Day 5 to Day 19 of gestation)

Post-exposure observation period: None

Vehicle Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]-

Remarks - Method

The study was designed to evaluate the effects of the test item on embryonic and foetal development. Females were euthanized before delivery, on gestation Day 20. All animals were subjected to a full external and internal examination and any macroscopic abnormalities were recorded. The ovaries and uteri of pregnant animals were removed, examined and recoded with number of corpora lutea, number, position and type of intrauterine implantation, foetal sex, external foetal appearance, foetal weight, placental weight and gravid uterus weight.

The dose level was determined based on the results of a previous toxicity study. In the previous study conducted by Harlan Laboratories Ltd (Project No. 41204722).

RESULTS

Group	Number of animals	Dose (mg/kg bw/day)	Mortality
control	8	0	0
Low dose	8	30	0
Mid dose	8	300	0
High dose	8	1000	0

Mortality and time to death

All animals survived to the scheduled necropsies.

Effects on dams

No signs of clinical toxicity were detected. No treatment related abnormalities were noted during the macroscopic examination of the pregnant animals at termination on Day 20 of gestation.

Effects on foetus

No treatment-related effects were noted for foetuses in treated animals when compared to control animals.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 1000 mg/kg bw/day in this study, based on the absence of treatment-related effects at any of the doses administered.

TEST FACILITY Harlan (2013b)

Appendix B: Environmental fate and ecotoxicological investigations

The robust summaries of the environmental fate and ecotoxicological studies submitted for the new chemical assessments of the chemical (NICNAS, 2013; 2014) are presented here.

B.1 Environmental fate

B.1.1 Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 A Ready Biodegradability: DOC Die-Away Test.
Inoculum	Activated sludge
Exposure Period	22 days
Auxiliary Solvent	None reported
Analytical Monitoring	TOC Analysis
Remarks - Method	The test was conducted according to the guidelines above using good laboratory practice (GLP). No significant deviations from the test guidelines were reported.

RESULTS

Test substance		Aniline	
Day	**% Degradation**	**Day**	**% Degradation**
1	-7	1	-5
3	6	5	95
14	95	14	97
22	102	22	100

Remarks - Results

All validity criteria for the test were satisfied. The reference compound, aniline, reached the 70% pass level by day 5 indicating the suitability of the inoculum. The toxicity control exceeded 35% biodegradation within 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after the cultivation period was 102% and it reached the pass level within the 10-day window. Therefore, the test substance is classified as readily biodegradable according to the OECD (301 A) guideline.

CONCLUSION

The notified chemical is readily biodegradable

TEST FACILITY	BASF (1999a)

B.2 Ecotoxicological investigations

B.2.1 Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sludge
Exposure Period	30 min
Concentration Range	Nominal: 1, 10, 100 mg/L
Actual:	Not measured
Remarks – Method	The test was conducted according to the guidelines above using good laboratory practice (GLP). No significant deviations from the test guidelines were reported.
RESULTS	
EC50	> 1000 mg/L at 30 min
NOEC	≥ 1000 mg/L at 30 min
Remarks – Results	All validity criteria for the test were satisfied.
CONCLUSION	The notified chemical is not inhibitory to microorganisms
TEST FACILITY	BASF (1999b)

References

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