Australian Government

Department of Health and Ageing

National Industrial Chemicals Notification and Assessment Scheme

INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP)

HUMAN HEALTH TIER II ASSESSMENT FOR

Ethanol, 2-butoxy-, acetate

CAS Registry Number: 112-07-2

PREFACE

As part of the reform regarding assessment of Existing Chemicals, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is implementing a new framework to address the human health and environmental impacts of industrial chemicals, not yet assessed, on the Australian Inventory of Chemical Substances (AICS).

The framework provides a more rapid, flexible and transparent approach for the assessment of existing chemicals.

The Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework was developed, with significant input from stakeholders, and will be applied in stages.

Stage One of this program, which will take four years, started 1 July 2012 and is examining 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This includes chemicals for which NICNAS already holds exposure information, chemicals identified as a concern or for which regulatory action has been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

This chemical/group of chemicals is/are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on the new program please visit: www.nicnas.gov.au

ACRONYMS & ABBREVIATIONS

ACToR	Aggregated Computational Toxicology Resource (US)
AICS	Australian Inventory of Chemical Substances
ASTDR	Agency for Toxic Substances and Disease Registry (US)
bw	bodyweight
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations (US)
CHO	Chinese hamster ovary
CosIng	Cosmetic Ingredients and Substances database (EU)
d	day
DNA	Deoxyribonucleic acid
EC	European Commission
EC3	Estimated concentration three
ECHA	European Chemicals Agency
ESIS	European Chemical Substances Information System
EU	European Union
EU RAR	European Union Risk Assessment Report
FDA	Food and Drug Administration (US)
FSANZ	Food Standards Australia and New Zealand
g	gram
g/mol	grams per mole
GHS	Globally Harmonized System of Classification and Labelling of Chemicals*
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPMT	Guinea Pig Maximisation Test
h	hour
HGPRT	hypoxanthine guanine phosphoribosyltransferase
HPV	high production volume
HSDB	Hazardous Substances Data Bank
HSIS	Hazardous Substances Information System
HVICL	High Volume Industrial Chemicals List
IARC	International Agency for Research on Cancer
INCHEM	International Programme on Chemical Safety (also known as IPCS)
INCI	International Nomenclature of Cosmetic Ingredients
ip	intraperitoneal
IRIS	Integrated Risk Information System (US)
IUCLID	International Uniform Chemical Information Database
iv	intravenous
kg	kilogram
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LCLo	lowest published lethal concentration
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
m^3	cubic metre
mg	milligram
mg/cm^3	milligrams per cubic centimetre
mg/kg bw/d	milligrams per kilogram bodyweight per day
min	minute
mL	millilitre
µg	microgram
µL	microlitre
(m)SDS	(material) Safety Data Sheet

NIOSH	National Institute for Occupational Safety and Health (US)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program (US)
OECD	Organisation for Economic Cooperation and Development
OEL	occupational exposure limit
PCBU	person conducting a business or undertaking
PEL	permissible exposure limit
PND	postnatal day
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
REACH	Registration Evaluation Authorisation of Chemicals (ECHA)
SD	Sprague Dawley
SIAP	SIDS Initial Assessment Profile (OECD)
SIAR	SIDS Initial Assessment Report (OECD)
SIDS	Screening Information Data Set (OECD)
SMILES	simplified molecular-input line-entry system
SPIN	Substances in Preparations In the Nordic countries
STEL	short-term exposure limits
STV	short-term value
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard**)
TCLo	lowest published toxic concentration
TEEL	temporary emergency exposure limits
TSCA	Toxic Substances Control Act (US EPA)
TG	test guideline
TGA	Therapeutic Goods Administration
TLV	threshold limit values
TWA	time weighted average
UN	United Nations
US	United States of America
US EPA	United States Environmental Protection Agency
WHS	Work, Health and Safety
wt	weight
w/w	weight per weight

Glossary

NICNAS uses the IPCS Risk Assessment Terminology (IPCS, 2004) glossary, which includes:
Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment; and
Part 2: IPCS Glossary of Key Exposure Assessment Terminology.
The IPCS Risk Assessment Terminology can be accessed at:
http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

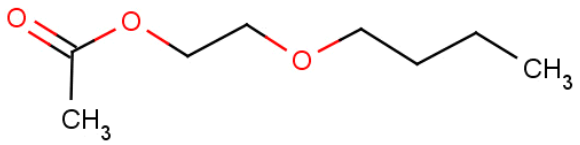
*Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Can be accessed at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

**The Poisons Standard (the SUSMP) can be accessed at: http://www.tga.gov.au/industry/scheduling-poisons-standard.htm

Ethanol, 2-butoxy-, acetate

CAS No: 112-07-2

Chemical Identity

Synonyms	Butyl glycol acetate Ethylene glycol, monobutyl ether acetate EGBEA Butyl cellosolve acetate 2-butoxyethanol acetate
Structural Formula	
Molecular Formula	C8H16O3
Molecular Weight (g/mol)	160.2
Appearance and Odour (where available)	Colourless liquid with a fruity odour.
SMILES	C(C)(=O)OCCOCCCC

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported commercial or domestic use including as a:

- coalescing agent; and
- solvent for paints, lacquers, adhesives and other materials.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR), the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal including the US Environmental Protection Agency (EPA) Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical is included in the CosIng database and US Personal Care Products Council INCI directory with the identified functions of solvent and masking. However, there is currently no documented use of the chemical in cosmetic products in the United States (Personal Care Products Council 2011).

The chemical has reported domestic use including in coatings and paints with reported concentrations below 20 % (EU RAR 2006), and as a cleaning agent. The chemical is reported to be present in a liquid sealant (concentration not specified), and a spray cleaning product up to a concentration of 5 % (Household Products Database, US Department of Health and Human Services).

The chemical has reported commercial use including:

- solvent in nitrocellulose lacquers, acrylic enamels, epoxy resins, and multicolour lacquers;
- as a solvent in paints and coatings;
- in adhesives and fillers;
- as a solvent in metal cleaning and screen printing; and
- in leather processing.

Restrictions

Australian

The chemical falls within the scope of 2-butoxyethanol and its acetates **except** in preparations containing 10 % or less of such substances, which are listed on Schedule 6 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for preparations containing more than 10 % glycol ether. Schedule 6 chemicals are labelled with "POISON". These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.

International

No known restrictions have been identified.

Existing Worker Health And Safety Controls

Hazard classification

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):
Xn; R20/21 (Acute toxicity).

Exposure standards

Australian

The chemical has an exposure standard of 133 mg/m³ (20 ppm) time weighted average (TWA) and a 333 mg/m³ (50 ppm) short-term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica):
An exposure limit (OEL, TWA, STEL, PEL or STV) of 65–333 mg/m³ (10–50 ppm) in different countries such as USA, Canada, Norway and Switzerland.

Health Hazard Information

The chemical (EGBEA) is expected to rapidly metabolise to 2-butoxyethanol (CAS No. 111-76-2), therefore data for 2-butoxyethanol are considered to represent the systemic toxicity of the chemical (EGBEA) and have been included in this report when no specific or valid data are available on EGBEA.

Toxicokinetics

Absorption of the chemical following inhalation and dermal exposure has been observed in animals and humans (ASTDR 2009; EURAR 2006; OECD 2006; REACH).

The chemical is expected to be widely distributed throughout the body, with no site of accumulation identified.

The chemical is expected to rapidly metabolise to 2-butoxyethanol and subsequently to 2-butoxyacetic acid (BAA), which is excreted in the urine.

Acute Toxicity

Oral

The chemical is of moderate to low acute toxicity in animal tests as evidenced by reported oral LD50s in rats of 1600–7000 mg/kg bw and in rabbits of approximately 940 mg/kg bw. Observed sub-lethal effects included haemolysis and associated lesions (ASTDR 2009; EURAR 2006; OECD 2006; REACH).

Dermal

The chemical is classified as hazardous with the risk phrase 'Harmful in contact with skin' (Xn; R21) in HSIS (Safe Work Australia). The data available generally support this classification.

In one study in rabbits, the median lethal dose (LD50) was reported to be an approximately 1500 mg/kg bw absorbed dose, which would correspond to an applied dose of between 4,766 and 5,957 mg/kg. Reported signs of toxicity include haemolysis and associated lesions (ASTDR 2009; EURAR 2006; OECD 2006; REACH). In another study for which limited information was available, an LD50 of 1580mg/kg was reported (REACH).

Inhalation

The chemical is currently classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in HSIS (Safe Work Australia). No lethality has been reported in acute inhalation studies following a single exposure (4–6 hours) to saturated vapour concentrations of the chemical (approximately 400 ppm). However, in one study 2/18 animals died after an eight hour exposure to saturated vapour. Mortalities were also reported in rabbits exposed to 400 ppm for one month, five days a week, four hours a day. Symptoms of haemolysis were observed in the majority of studies (ASTDR 2009; EURAR 2006; OECD 2006; REACH). No studies on aerosols of the chemicals have been identified.

While the available data do not support the classification (LC50 not reached at the saturated vapour concentration), in the absence of more comprehensive information, there is insufficient evidence to recommend removal of the current HSIS classification.

Corrosion / Irritation

Skin irritation

The chemical is reported to slightly irritate skin in animal studies (ASTDR 2009; EURAR 2006; REACH). The effects were not sufficient to warrant a hazard classification.

Eye irritation

The chemical is reported to slightly irritate eyes in animal studies (ASTDR 2009; EURAR 2006; REACH). The effects were not sufficient to warrant a hazard classification.

Respiratory irritation

No signs of significant respiratory irritation were observed in acute and repeat-dose inhalation studies (ASTDR 2009; EURAR 2006).

Although the metabolite 2-butoxyethanol is known to cause respiratory irritation at high concentrations, this is unlikely at atmospheric vapour concentrations (NICNAS 1996). In addition, the chemical is less irritating than this metabolite (OECD 2006). Therefore, the chemical is not expected to act as a respiratory tract irritant.

Sensitisation

Skin sensitisation

The available data support a conclusion that the chemical is not a skin sensitiser. The chemical produced negative results in a Buehler test (EURAR 2006). In addition, the metabolite 2-butoxyethanol is not a sensitiser (NICNAS 1996).

Repeat Dose Toxicity

Oral

No data are available for the chemical. The metabolite 2-butoxyethanol caused haematological effects (decrease in haemoglobin concentration, red blood cell count, increase in mean cell volume—MCV, and mean cell haemoglobin—MCH) in repeat-dose oral toxicity studies in rats, with a recorded lowest observed adverse effect level (LOAEL) of 82 mg/kg bw/day (NICNAS 1996; EURAR 2006).

Dermal

No data are available for the chemical. No significant toxicological effects were observed in a 90-day repeat-dose dermal toxicity study in rabbits for the metabolite 2-butoxyethanol (NOAEL of 150 mg/kg bw/day) (NICNAS 1996; EURAR 2006).

Inhalation

A number of repeat-dose inhalation studies (four weeks to 10 months) were available for the chemical across several species (rats, mice, rabbits and guinea pigs). Signs of haematotoxicity and associated lesions were seen in all species except guinea pigs (lowest observed adverse effect concentration (LOAEC) 100–400 ppm. These studies have a number of deviations from OECD test guidelines, hence the LOAEC may not be reliable (EURAR 2006).

The critical health effect observed in animal studies with the metabolite 2-butoxyethanol is haemolysis of the blood cells. The severity of the effect differs markedly between species; rats and mice are the most sensitive (lowest NOAEC of 24.6 ppm) (NICNAS 1996; EURAR 2006).

Genotoxicity

No data are available for the chemical. In vitro genotoxicity studies generally yield a negative result for the metabolite 2-butoxyethanol and it is not considered genotoxic (ASTDR 2009; EURAR 2006; NICNAS 1996).

Carcinogenicity

No carcinogenicity data are available for the chemical.

Two carcinogenicity studies in rats and mice (2-year, via inhalation) are available for the metabolite 2-butoxyethanol. A significant increase in the incidence of liver haemangiosarcomas was seen in male mice, and forestomach tumours were observed in female mice. However, several international reviews of these data (OECD, United States and the European Union) have concluded that the results of these studies are not relevant to humans and that 2-butoxyethanol is not considered a human carcinogen (OECD 2006; SCHER 2008).

Reproductive and developmental toxicity

No specific reproductive or developmental toxicity studies were available for the chemical. The reproductive effects observed with certain short-chain monoethylene glycol ethers have not been demonstrated with the metabolite 2-butoxyethanol. Similarly, no evidence of teratogenicity was observed with 2-butoxyethanol (NICNAS 1996).

Risk Characterisation

Critical Health Effects

The critical health effects for risk assessment are acute toxicity through all routes of exposure.

Although the chemical is also reported to cause haemolysis and associated organ toxicity in rats, the severity of effects differs markedly between species, with humans appearing to be the least sensitive. Based on modelled data for the metabolite 2-butoxyethanol, it is considered unlikely that haemolytic blood concentrations would be reached in humans through inhalation (NICNAS 1996; OECD 2006).

Public Risk Characterisation

Although the use of this chemical in domestic products in Australia is not known, the chemical is reported to be used in domestic products overseas at concentrations up to 20 %. The chemical is currently listed on Schedule 6 of the Poisons Schedule for preparations containing more than 10 % of the chemical. At concentrations greater than 10 %, a number of first aid instructions and safety directions relating to skin and eye contact apply.

The margins of exposure of >100, estimated in a risk assessment conducted internationally for the chemical (EU RAR 2006), indicate that the chemical does not pose an unreasonable risk to the public when present in paint at a concentration of 20 %. The estimated margins of exposure are considered

applicable in the Australian context.

In addition, a NICNAS assessment of the metabolite 2-butoxyethanol concluded that the public risk from using domestic cleaning products was minimal due to the low concentration of 2-butoxyethanol in most domestic cleaning products.

Based on international information about use of the chemical in cosmetics (see **International uses** above), significant use of the chemical in cosmetics is not anticipated in Australia and therefore the risk to public health is not considered to be unreasonable.

Overall, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety. However, a modification to the entry in the SUSMP may be appropriate (refer to **Recommendation Section**).

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur when using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute health effects and possible haemolytic effects at high concentrations, the chemical may pose an unreasonable risk to workers if adequate control measures to minimise dermal and inhalation exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU), e.g. employer, at a workplace has adequate information to determine appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment is adopted for the classification, and labelling of the chemical and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Further risk management is not considered necessary for public safety. However, a modification to the entry in the SUSMP may be appropriate. Consideration should be given to the following:

- the chemical does not pose an unreasonable risk to the public when present in domestic products at known use concentrations (20 %); and
- any review of the entry in the SUSMP should form part of a review of the entries for all ethylene glycol monoalkylethers and their acetates.

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of the physical and environmental hazards.

	Approved Criteria (HSIS)[a]	*GHS Classification*
Acute Toxicity	Harmful if swallowed (Xn; R22) Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

* Existing Hazard Classification. No change recommended to this classification.

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate, or sufficiently minimise, risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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