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

Carbamic acid, butyl-, 3-iodo-2-propynyl ester

CAS Registry Number: 55406-53-6

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

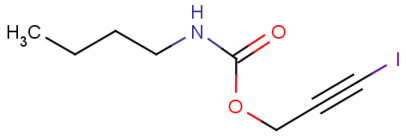
*Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Can be accessed at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

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

Carbamic acid, butyl-, 3-iodo-2-propynyl ester

CAS No: 55406-53-6

Chemical Identity

Synonyms	3-Iodo-2-propynyl butylcarbamate Iodopropynyl butylcarbamate Butyl-3-iodo-2-propynylcarbamate Iodocarb IPBC
Structural Formula	
Molecular Formula	C8H12INO2
Molecular Weight (g/mol)	281.1 g/moles
Appearance and Odour (where available)	An organic carbamate compound;, it is a white or slightly off white crystalline powder with a sharp pungent odour. It is highly soluble in organic solvents and moderately soluble in water.
SMILES	C(I)#CCOC(=O)NCCCC

Import, Manufacture and Use

Australian

The following industrial uses have been identified in Australia.

The chemical has reported cosmetic use as:
- preservative in baby wipes.

The following non-industrial uses have been identified in Australia:
- an approved active constituent in pesticides by the Australian Pesticides and Veterinary Medicines Authority (APVMA).

International

The following International uses have been identified via Galleria Chemica, Substances in Preparations In the Nordic countries (SPIN), CosIng, Hazardous Substances Database (HSDB) and European Chemicals Agency (ECHA).

The chemical is used as a fungicide and antimicrobial in both industrial processes and residential settings.

The chemical has reported cosmetic use as:
- a preservative in cosmetic products in both leave-on and rinse-off cosmetic/personal care products such as shampoos, hair conditioners, shower gels, rinses, creams, lotions, mascaras, liquid and powder type cosmetics, eye products, bubble baths, sunscreens, hair dyes, cleansing agents, masks, tanning preparations, wipes and towelettes. It was reported to be used with typical concentration ranging from 0.005% - 0.1% (Lanigan, 1998). The chemical is also reported to be present in a range of cosmetic products (rinse-off and leave-on) at concentrations ranging between 0.1 - 5%, with majority at <0.5% (Household Products Database, HHPD).

The chemical has reported domestic use. It is reported to be present in a range of domestic (home maintenance) products at concentrations ranging between 0.1 - 15%, with majority at 0.2% (Household Products Database, HHPD). Domestic uses identified are:

- paints, lacquers and varnishes;
- cleaning and washing agents;
- adhesives and binding agents;
- corrosion inhibitors;
- fillers; and
- surface treatment.

The chemical has reported commercial use as:
- heating, ventilation and air conditioning (HVAC) ducts applications to control mould and fungi;
- wood preservative;
- can preservative;
- film preservative;
- fibre, leather, rubber and polymerised materials preservatives;
- masonry preservatives;
- metalworking preservatives;
- metal cutting fluids; and
- plastics manufacturing.

Restrictions

Australian

The chemical is listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in:
Schedule 5 - in preparations containing 10% or less except in aqueous preparations containing 10% or less; and
Schedule 6 - except when included in schedule 5 or in aqueous preparations containing 10% or less.

International

European Union (EU): The use of the chemical in cosmetics in the European Union is subject to the restrictions described in EU Regulation Annex V (Ref 56). This preservative may be used in cosmetics and personal care products at a maximum concentration of 0.02% in rinse-off products, and at 0.01% in leave-on products, except in deodorant/antiperspirant products in which the limit is 0.0075%. It is not to be used for oral hygiene and lip-care products, or in products intended to be used on a large part of the body, such as body lotion. With the exception of bath products and shampoo, it is not to be used in products intended for children under 3 years of age.

It is noted that these restrictions were put in place based on the Scientific Committee on Cosmetic Products and non-food products intended for consumers (SCCNFP) opinion (SCCNFP/0826/04) that the daily bioavailable intake of iodine from cosmetic products should not exceed 20% of the recommended daily intake of 150 µg. This is, for example, equivalent to approximately 0.002% iodopropynyl butylcarbamate (IPBC) in all cosmetic products at a daily use of 18 g and at a percutaneous absorption rate of 20%. This opinion considered additional information available (to date) regarding health effects from the use of iodine from cosmetics. It is noted that the restrictions for infants were put into place based on the uncertainty around possible iodine uptake from the use of products containing IPBC.

Prior to this, the SCCNFP/0193/99 opinion on the use of IPBC as a preservative was adopted in 1999, which allowed a concentration up to 0.05% of IPBC in cosmetics. It was not to be used in oral hygiene and lipcare products and the use of the substance in leave-on products which contain more than 0.02 % necessitated a warning label: "Contains Iodine". Evaluation of acute toxicity (oral, dermal), skin and mucous membrane irritation, sub-chronic toxicity (oral), sensitisation, reproductive toxicity (oral), genotoxicity, percutaneous absorption, dose-dependent adverse effects (cholinesterase activity inhibition) and possible influences of IPBC (especially its iodine contents) on endocrine functions showed that the chemical can be safely used under the conditions stated in the Opinion. It was concluded that in general population 0.05% concentration will not cause adverse effects from the absorption of iodine (SCCNFP,

1999).

US Cosmetic Ingredient Review (CIR), 1998: The CIR considers the chemical to be safe for use at concentrations ≤ 0.1%. This concentration was based on acute inhalation toxicity, potential for mild dermal irritation at concentrations of 0.5% and the absence of any data on comedogenicity at concentrations higher than 0.1% in clinical tests. Based on concerns about inhalation toxicity, it was concluded that it should not be included in cosmetics and personal care products meant to be aerosolised. As the highest concentration tested for comedogenicity was 0.1%, the CIR Expert Panel considered this concentration to be the highest for which the available data would support safety (Lanigan, 1998).

It is noted that the CIR report did not consider any data regarding the health effects from iodine in the chemical. Additionally, the sensitisation data used for the assessment were dated prior to 1995 and since then several reports have been made available regarding the sensitisation potential of this chemical.

Existing Worker Health And Safety Controls

Hazard classification

The chemical is currently classified on the Hazardous Substances Information System (HSIS) (may be accessed at http://hsis.safeworkaustralia.gov.au/HazardousSubstance) with following:
Xn: R22 (Acute toxicity); and
Xi: R36/38 (Irritation).

Exposure standards

Australian

There are no exposure standards in Australia.

International

German exposure limit for the chemical is 0.01 mL/m³ (0.12 mg/m³) for pregnancy risk group classification Category C. This is consistent with exposure limits in Switzerland. A sensitisation notation is reported to apply in both these countries (Galleria Chemica).

Health Hazard Information

Toxicokinetics

Absorption, Distribution & Excretion:

The chemical was administered orally in 0.5% carboxymethylcellulose to groups of male and female Crl:CD/BR rats. Groups of 5 male and 5 female rats (groups A and B) received either a single oral high dose of radiolabelled IPBC (125 mg/kg) or a repeated low oral dose of non-radiolabelled IPBC followed by a single radiolabelled dose (20 mg/kg). Separate groups of rats (9/sex/group, groups C and D) received single oral doses (20 and 125 mg/kg) of radiolabelled IPBC, and 3 rats/sex underwent necropsy at 2, 4, and 120 hours post-dose for determination of tissue distribution of radioactivity. Urine, faeces and expired air were collected at 24 hr intervals for groups A and B, while urine and faeces were collected from groups C and D. Absorption of test chemical at the low and high dose was between 80-90% for all dose groups, as suggested by excretion data showing the majority of a dose eliminated through urine or exhaled air. Excretion of IPBC-derived radioactivity was mainly via the urine, with between 50-70% of an administered dose excreted by this route at 168 hours post-dose. Faeces was a minor route of excretion in all dose groups (4-7% of the administered dose), while radiolabelled CO_2 constituted between 18-24% of the administered dose. Repeated low oral dosing or a single high oral dose appeared to result in a decrease in the percentage of radioactivity excreted as ^{14}C compared to a single low dose (US EPA, 1997).

In skin penetration studies using human cadaver skin, 53±14% of radiolabelled IPBC (from a 0.1% solution) penetrated the skin and 14±5% evaporated from the skin surface. It is noted that studies with human cadaver skin do not provide information on the influence of metabolism on the penetration of IPBC. Studies using viable skin will be more useful in assessing the true penetration of IPBC (Lanigan,

1998).

Metabolism/Metabolites:
IPBC undergoes reductive dehalogenation followed by dealkylation to form two major metabolites (referred to as URM-9 and URM-10). In addition, de-carboxylation following reductive dehalogenation yields carbon dioxide. Various other metabolites formed from dehalogenation are glucuronidated and constitute minor metabolites of IPBC (US EPA, 1997).

Iodine release:
There is a possibility of the liberation of free iodine from the use of cosmetics containing this chemical and consequently unwanted interactions with the thyroid hormone system. The recommended daily intake of iodine in Australia is 150 µg/day. A Food Standards Australia and New Zealand (FSANZ) report (2007) published on the safety and risk assessment of iodine fortification adopted a LOAEL of 1700 µg/day and derived an Upper Intake Level (UL) of 1100 µg/day for iodine. The ULs for iodine are not considered absolute thresholds for toxicity but rather represent intake limits, which provide a comfortable margin of safety for the Australian population. It is indicated that the general healthy population may exceed the UL by 2-3 fold without any apparent adverse consequences. Moreover, the overall potential for adverse effects in the young children that are estimated to exceed the UL for iodine is considered low. This and the reversible nature of the end point, means that small additional intakes are unlikely to represent a health and safety risk to young children, although a reduced margin of safety exists (FSANZ, 2007).

Acute Toxicity

Oral
The chemical is currently classified with the risk phrase 'Harmful if swallowed' (Xn; R22) in Australia. The data available support this classification.

The chemical was found to be of moderate acute toxicity by the oral route. The acute oral lethal dose, 50% (LD50) after a 14-day observation period in female and male rats was 1100 mg/kg and 1795 mg/kg respectively. In another study rats given 1000-1500 mg/kg IPBC had soft faeces, urine stains, rough coats, and/or slight depression and red stains on the nose and eye area. Cosmetic formulations containing 0.01-0.0125% IPBC had an acute oral LD50 > 10,000 mg/kg bw in rats (HSDB).

Dermal
The chemical was found to be of low acute toxicity by the dermal route of exposure. The acute dermal LD50 in rabbits was found to be >2,000 mg/kg bw. IPBC caused erythema and oedema at the treatment sites in all rabbits (Galleria Chemica, 2012).

Inhalation
In acute toxicity studies, the chemical was found to be of high acute toxicity by the inhalation route. The average acute inhalation lethal dose, 50% (LC50) in rats was 0.68 mg/L (dust) and 0.78 mg/L (aerosol). Rats administered with IPBC as dusts and liquid aerosols had decreased activity, eye closure and excessive lacrimation. Survivors had laboured breathing, gasping and secretory discharges after exposure. At necropsy, oedema, emphysema and reddened lungs were observed (Lanigan, 1998).

The chemical is not currently classified based on its acute inhalation toxicity. The data available support the need for classification of the chemical with the risk phrase 'Toxic by inhalation' (T; R23).

Corrosion / Irritation

Skin irritation
The chemical is currently classified with the risk phrase 'Irritating to skin' (Xi; R38) in Australia. The highest quality data available do not support this classification with the chemical reported to be slightly irritating in a OECD guideline 404 compliant study (Galleria Chemica, 2012; ECHA, 2011). Irritation was evident in the acute dermal study and the subchronic dermal toxicity study. In addition, mild irritation has been observed in human clinical studies (see below). The current data, in the absence of

more comprehensive information, are not sufficient to recommend removal of the current HSIS classification.

Eye irritation

The chemical is considered a severe eye irritant. In a primary eye irritation study in rabbits, technical grade IPBC was severely irritating to the eyes of white rabbits, with corneal opacity and corneal vascularisation reported in unwashed eyes by day 21 post-treatment. Cosmetic formulations containing 0.1 - 0.015% IPBC produced slight conjunctival redness in rabbits (Lanigan RS, 1998).

The chemical is currently classified with the risk phrase 'Irritating to eyes' (Xi; R36) in Australia. However, the data available indicate the chemical as a severe eye irritant. Therefore, the existing classification requires amendment.

Respiratory irritation

Clinical signs noted during the acute inhalation study summarised above such as laboured breathing and gasping as well as the findings in the lungs on gross necropsy are considered to be indicative for an irritant effect on the respiratory tract.

In a repeat dose inhalation study summarised below, the predominant effect was directed toward the larynx of exposed animals.

The data available support the need for classification of the chemical with the risk phrase 'Irritating to respiratory system' (Xi; R37).

Observation in humans

The chemical was found to be mildly irritating but not sensitising in a clinical study done between 1998 and 2008 by the North American Contact Dermatitis Group (NACDG) using 0.1% IPBC and/or 0.5% in petrolatum. For IPBC-positive patients, the most frequent sites of dermatitis were scattered generalised body distribution and on the hands, and arms. The majority (0.5%) of relevant reactions were due to personal care products (Warshaw et al., 2010).

In another clinical study, a 4% cosmetic formulation containing 0.0125% IPBC was mildly irritating when applied under occlusive patches for 24 hours in a primary irritation study. Erythema without oedema was observed (Lanigan et al., 1998).

Significant irritation was not reported in 5- and 21-day cumulative irritation studies that tested 0.01 - 0.0125% IPBC in formulation (Lanigan et al., 1998).

Sensitisation

Skin sensitisation

The sensitising potential of the chemical was studied in a local lymph node assay (LLNA) and was classified as a moderate-to-strong sensitiser based on the EC3 value of 0.87%. This was also confirmed by an increase in weight of the single lymph nodes (Siebert, 2004).

In a Guinea Pig Maximisation Test (GPMT), 6 out of 19 animals showed a positive response to the chemical when 1 and 3 % IPBC was used for induction and 0.5% was used for challenge (Zissu 2002). In another 2001 GPMT performed according to OECD TG 406, 9 out of 10 animals showed a positive response to IPBC when 5% IPBC was used as a challenge and 1% and 6% (the highest non-irritating concentration) used for intradermal and topical induction, respectively (ECHA, 2011). IPBC showed positive reactions in two other non-key GPMT studies. However, the studies are of limited value as no details on the dose selection for the lowest irritating concentrations for induction and the highest non-irritating concentrations used as a challenge were provided.

In a dermal sensitisation study, IPBC at a concentration of 0.32% produced no evidence of sensitisation in male and female guinea pigs. No data are available on the raw chemical (100%) or a higher

concentration of the chemical (US EPA, 1997). However, due to a lack of detailed information on the dose selection for the lowest irritating concentrations for induction and the highest non-irritating concentrations for challenge, the study is of limited value.

In a Buehler test performed according to OECD TG 406, IPBC showed no skin sensitising potential. No other details were provided (ECHA, 2011).

In conclusion, IPBC is considered to be a skin sensitiser based on the positive results seen in the LLNA and GPMT studies. One study showed the Buehler test to be negative; however, the Buehler test is generally considered not as sensitive as the GPMT. The positive data are supported by the human case reports detailed below.

Observation in humans

There are several reports available on the sensitisation potential of IPBC in humans. Recently, it has been described as an emerging contact allergen based on its increasing use in cosmetics (Davies and Johnston, 2011). Although the risk appears to be low at concentrations up to 0.1%, IPBC-induced contact allergy may increase with increasing availability of IPBC-containing cosmetic products or at higher concentrations or following longer term exposures (Badreshia and Marks, 2002 and Lanigan, 1998).

In a report on the sensitisation potential of IPBC in humans, three positive reactions (out of 311 patients from allergenicity hospitals) to patch tests with 0.1% IPBC in petrolatum were observed (ECHA, 2012). In a recent study by the same authors, four additional patients with IPBC contact allergy were diagnosed among a total number of 3168 persons patch tested with IPBC (0.1% in petrolatum) (ECHA, 2012). In another report, three out of 312 patients showed reactions to patch tests with 0.01 to 0.1% IPBC in petrolatum; one patient had reactions interpreted as allergic (ECHA, 2012). Another study reported that five metal workers out of 23 tested showed positive patch tests to a variety of metalworking fluids containing IPBC at concentrations from 0.5 to 2.5% (ECHA, 2012).

In another separate case study report, a 34-year old female worker at a paint factory developed dermatitis on exposed skin areas to a product containing 0.01% IPBC (HSDB). Another case study reported a 63-year old man developing severe perianal and palmar contact dermatitis caused by sensitisation from using moist sanitary wipes containing IPBC (HSDB).

Among 4883 persons patch-tested with IPBC (0.1% in petrolatum), 0.3% of the patients had positive skin reactions and 0.5% had doubtful reactions at day 3. Patients exposed for 24 h (n = 1814) reacted less frequently (0.1%) than the remaining patients exposed for 48 h (0.5%). The authors noted that the large number of doubtful reactions can possibly be due to the irritant nature of the chemical and not using a higher concentration to elicit an allergic response (Schnuch et al., 2002).

In an extension of the above study, the same authors found that the risk of sensitisation to the chemical was not negligible in a study done with 3541 leave-on products containing preservatives including IPBC, at concentrations >0.5%. Frequency of sensitisation to preservatives was analysed on patients' data available between 2006 and 2009. Iodopropynyl butylcarbamate was identified as being associated with a higher risk within the preservatives tested. The authors were of the opinion that frequent use of certain preservatives or high use concentrations may lead to higher frequencies of sensitisation (Schnuch et al., 2011).

The recent available human data supports the findings from the animal studies that IPBC is a skin sensitiser. Based on the positive results in the human patch tests and the positive animal studies, the chemical is recommended for classification with the risk phrase 'May cause sensitisation by skin contact' (Xi; R43).

Repeat Dose Toxicity

Oral

In a subchronic oral toxicity study, male and female Sprague-Dawley (SD) rats received IPBC (98% pure) by gavage for 13 weeks at doses of 0, 20, 50, and 125 mg/kg bw/day. An additional satellite group

received 125 mg/kg bw/day for 13 weeks, and then was held for a 28-day observation period following the 13-week dosing regimen. Body weight gain was decreased at the 125 mg/kg bw/day dose level, by 19% in male rats for weeks 1-13 of the study, and by 12% in female rats over the same period. Absolute liver weight was increased by 20% in male rats at the 125 mg/kg/day dose, and by 31% in female rats at this dose level. Liver to body weight ratio was significantly increased by approximately 31% in both male and female rats at the 125 mg/kg/day dose level, while kidney to body weight ratio in female rats was increased by 18% at the 125 mg/kg/day dose level. Clinical signs such as excess salivation, lethargy, wheezing and epistaxis were noted in males at 50 and 125 mg/kg and in females at 125 mg/kg doses. The systemic no-observed effect level (NOEL) was considered to be 20 mg/kg/day, while the systemic lowest observed effect level (LOEL) was considered to be 50 mg/kg/day based on increased liver to body weight ratio (US EPA, 1997).

In a separate 78-week mice study, a NOEL of <20 mg/kg/day and the LOEL of 20 mg/kg/day were determined, based on the increased incidence in enlarged thyroids accompanied by foci of small vacuolated cells most likely of follicular origin and general follicular enlargement at the highest dose (150 mg/kg bw/d). No adenomas (as expected in the case of a break of the pituitary, thyroid, hypothalamic circuit) were observed. The toxicological significance of these findings in thyroids remains unclear (US EPA, 1997).

In a 2-year chronic toxicity/carcinogenicity study, technical grade IPBC (98.68%) was administered to male and female Sprague Dawley rats (50/sex/group) at dose levels of 0, 20, 40, and 80 mg/kg/day for 104 weeks. At 52 weeks, 15/sex/dose animals were necropsied to assess chronic toxicity. At 104 weeks, 50/sex/dose animals were necropsied to assess carcinogenicity. At 52 weeks, macropathology changes were seen in the stomach at >40 mg/kg/day in both sexes. Increased liver weights were observed at 80 mg/kg/day at 52 weeks in both sexes as well. At the 80 mg/kg/day dose level, body weight gain decrements of 20% and 15% were observed in male and female rats, respectively, during the first 13 weeks of the study. At study termination, body weight gain in male rats at the 80 mg/kg/day dose level was decreased to 71% of control, and in female rats, to 76% of control. Significant changes in serum chemistry were observed in male rats at the 80 mg/kg/day dose, as were significant non-neoplastic changes in the stomach (submucosal oedema, submucosal inflammation, acanthosis, hyperkeratosis, ulceration, and basal cell proliferation) in both sexes. The non-neoplastic changes in the stomach were considered the result of chronic irritation, and were not considered indicative of a neoplastic response. The systemic NOEL was determined to be <20 mg/kg/day (lowest dose tested), and the systemic LOEL was determined to be 20 mg/kg/day, based on decreased body weight gain in male rats. The 80 mg/kg/day dose level was considered adequate for testing of carcinogenic potential of IPBC, based upon decreased body weight gain in male and female rats (US EPA, 1997). No evidence of carcinogenicity was evident.

Based on the available information no hazard classification for repeat dose oral toxicity is recommended.

Dermal

In a subchronic dermal toxicity study, male and female SD rats (10/sex/dose) received dermal doses of 50, 200, and 500 mg/kg/day IPBC technical grade (97.5%) to the shaved skin for 91 days (for five days a week, six hours per day). At the 500 mg/kg/day dose, decreased body weight (4-6%) and weight gain (11%) were observed in male rats, but not in female rats. In female rats, significant increases in haemoglobin, haematocrit, and eosinophils were observed at the 500 mg/kg/day dose level. Reticulocytes as a percentage of red cells were decreased in the 50 and 200 mg/kg/day dose groups but not at the 500 mg/kg/day dose level. Decreased serum glucose and decreased serum creatinine were observed in male rats at 500 mg/kg/day. Minimal to mild skin irritation (acanthosis and hyperkeratosis) are observed in both male and female rats. Increased serum gamma-glutamyl transferase (24% increase) was observed in female rats. At the 200 mg/kg/day dose, decreased serum glucose was observed in male rats, as was minimal to mild acanthosis and hyperkeratosis in male and female rats. Food consumption was intermittently statistically decreased in males at > 200 mg/kg. Females in this study showed inhibition of plasma cholinesterase at 500 mg/k/day test article, which may have been the result of either direct liver toxicity or inhibition of cholinesterase itself. Based upon the results of this study, the dermal NOEL is 50 mg/kg/day, the systemic LOEL is 200 mg/kg/day for male and female rats (US EPA, 1997).

Based on the available information no hazard classification for repeat dose dermal toxicity is recommended.

Inhalation

In 13-week repeat dose inhalation toxicity study in male and female SD rats the no observed adverse effect concentration (NOAEC) for the chemical was reported to be 1.16 mg/m³. The predominant effect was directed toward the larynx of exposed animals. Histopathological findings in the animals exposed to 6.7 mg/m³ (highest dose) included necrosis in the ventral cartilage, epithelial hyperplasia in the ventral region and hyperplasia or squamous metaplasia in the ventrolateral region. These effects were considered as a local and not a systemic effect. No functional changes or any organ dysfunction were observed in treated animals as a consequence of the irritation effects in the laryngeal region (ECHA, 2011).

Based on the available information no hazard classification for repeat dose inhalation toxicity is recommended, however a classification for respiratory irritation is warranted.

Genotoxicity

In a mutagenicity study, technical grade IPBC was tested for the ability to cause mutations in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100. In the five strains used, IPBC was found to be non-mutagenic in the presence or absence of metabolic activation at the concentrations tested, 1-500 µg/plate. In a micronucleus assay in mice, IPBC at doses of 200, 600, and 2000 mg/kg did not induce any significant increase of the polychromatic erythrocytes (PCE) containing micronuclei in the treated mice when compared to that of the vehicle control mice. In two independent unscheduled DNA synthesis (UDS) assays in primary rat hepatocytes, eight doses of IPBC ranging from 3.0 to 13.5 µg/mL did not cause an appreciable increase in mean net nuclear grain counts. Doses >13.5 µg/mL were cytotoxic, supporting the conclusion that IPBC induced cytotoxicity but no genotoxicity in this assay (US EPA, 1997).

Based on the weight of evidence from the above in vitro and in vivo genotoxicity studies, no classification is recommended.

Carcinogenicity

The chemical was not carcinogenic in rats and mice up to and including the highest dose levels (80 and 150 mg/kg bw/d) for rats and mice. In the mice carcinogenicity study, an increased incidence of hepatocellular adenomas in high dose males (11/50) is not considered to be of biological relevance. Based on the available study no hazard classification is recommended for carcinogenicity.

Reproductive and developmental toxicity

In a 2-generation reproductive toxicity study, rats were treated via gavage at 0, 10, 30, and 100 mg/kg bw/d. A reduced fertility/mating index was observed in F0 parents at 100 mg/kg bw/d. Reduced live birth index was noted in F1 pups at 100 mg/kg bw/d, and reduced viability index and cumulative survival index in F1 pups at 30 and 100 mg/kg bw/d. Mean birth pup body weight was reduced in F1 females at 100 mg/kg bw/d, mean pup body weight at day 4 and 21 post partum in both sexes of F1 100 mg/kg bw/d, and mean pup body weight was statistically significantly reduced on day 21 post partum in F2 females at 30 mg/kg bw/d. An increased incidence of pups without milk in the stomach and/or bitten or cannibalised pups was noted at 30 and 100 mg/kg bw/d. Effects in pups were noted only at dose levels that also resulted in maternal toxicity (ECHA, 2011).

In an another 2-generation reproductive toxicity study that was conducted in male and female SD rats, technical grade IPBC was administered over two generations at doses of 0, 120, 300, and 750 ppm (0, 6, 15, and 37.5 mg/kg/day). Reduced body weight and food consumption were observed for P and F1 males during the premating period at the 37.5 mg/kg/day dose. During the same period, P males (300 ppm onwards) and F_1 males (750 ppm) showed reduced body weight gains. No treatment related effects were observed in clinical condition, necropsy findings, fertility, mating performance, postnatal viability, or postnatal growth. Physical and functional development were similar to controls. A decreased mean live birth index was reported for P_1 and F_1 generations at the highest dose. No adverse effects on reproductive indices or mating performance were observed at any dose level. The NOEL for both parental and

offspring toxicity was determined to be 37.5 mg/kg/day. No other maternal effects were reported. (US EPA, 1997).

An analytical report showed a considerable decline in the stability of IPBC in the diet over one month, especially for the high concentrations. Therefore, this study is not considered adequate for the evaluation of a reproductive toxic potential of IPBC and can only be used as a supporting study (ECHA, 2011).

The developmental toxicity of IPBC was assessed in pregnant SD rats on gestation days six through to 15 by oral administration of the test chemical at doses of 0, 20, 50, and 125 mg/kg/day. Maternal toxicity reduced body weight gain during dosing was observed at the 125 mg/kg/day dose level. Developmental toxicity consisted of an increased incidence of skeletal abnormalities at the 125 mg/kg/day dose level, which was stated to be caused by maternal effects. The maternal toxicity NOEL was determined to be 50 mg/kg/day, based on reduced body weight gain. The developmental toxicity NOEL was determined to be 50 mg/kg/day, based on incompletely ossified frontal skull bones and pelvic girdles (US EPA, 1997).

The developmental toxicity of IPBC was also assessed in rabbits on gestation days six through 15 by oral administration of the test chemical at doses of 0, 10, 20 and 40mg/kg bw/day via gavage mg/kg/day. There were no treatment-related effects on pregnancy data or foetal development including teratogenicity (ECHA, 2011).

Overall the chemical is not considered a reproductive or developmental toxin. Based on the available data, no classification is recommended.

Other Health Effects

Neurotoxicity

IPBC was not neurotoxic when administered via the oral route. A NOEL of 300 mg/kg/day was noted based on decreases in locomotor activity (HSBD).

The absence of neurotoxic effects is supported by the repeat dose inhalation study and carcinogenicity studies which all investigated RBC and brain cholinesterase inhibition (ECHA, 2011).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are acute toxicity via the oral and inhalation route of exposure, respiratory irritation, severe eye irritation, skin irritation and skin sensitisation.

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that may contain IPBC, the main route of public exposure to IPBC is expected to be through dermal exposure as well as inhalation exposure to products applied as aerosols and potential oral exposure to lip and oral hygiene products.

The characterised critical health effects have the potential to pose an unreasonable risk under the uses identified. The risks could be mitigated by implementation of concentration limits and restriction of uses to limit inhalation exposure, as supported in the SCCNFP and CIR Opinions and the data published in this report under hazards.

In relation to the potential adverse effects from the liberation of free iodine from the chemical, calculations using Australian food iodine intake data from FSANZ indicate that the risk associated with the use of this chemical is not high if concentrations similar to those reported as in use overseas (up to 0.1%) are considered. Implementing control levels similar to these will control the risk associated with iodine imbalance.

Occupational Risk Characterisation

Occupational exposure to IPBC may occur through inhalation (of powder) and dermal contact where it is produced, stored and when formulating products. Accidental eye exposure is also possible when handling

raw material (powder) at work places.

Worker exposure may also occur during use of the formulated products containing the chemical (at lower concentrations) such as paints, metal working fluid and wood preservatives.

Given the critical health effects, there is a risk to workers if adequate control measures to minimise occupational exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls. The existing hazard classification to the chemical needs amendment to indicate inhalation hazard (acute toxicity and irritation), severe eye irritation and skin sensitisation effects.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend the chemical to be risk managed for public safety from the potential use in cosmetics and/or domestic products through scheduling, and occupational health and safety through classification and labelling.

The chemical is considered to be sufficiently assessed at Tier II subject to implementation of risk management recommendations.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that the concentration of IPBC in cosmetics/personal care products and domestic products be restricted and that the restriction of the use in products intended to be aerosolised is also considered. Exemptions to scheduling may be applicable at low concentrations. Decisions on scheduling should take into account opinions published by SCCNFP (1999, 2004), CIR (Lanigan, 1998) and the more recent sensitisation data summarised in this report and the Harmonised Classification and Labelling report for the chemical (ECHA, 2011).

Work Health and Safety

The chemical is recommended for classification and labelling under the current Approved Criteria and adopted Globally Harmonised System (GHS) as below. These do not consider classification of physical hazards and environmental hazards.

	Approved Criteria (HSIS)[a]	*GHS Classification*
Acute Toxicity	Harmful if swallowed (Xn; R22)* Toxic by inhalation (T; R23)	Harmful if swallowed - Cat. 4 (H302) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

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

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

Advice for consumers

The chemical or products containing the chemical should be used according to label instructions.

Advice for industry

Work Health and Safety (WHS) legislation in each Australian state and territory imposes obligations on manufacturers and importers of hazardous chemicals to ensure that the chemicals are correctly classified, correctly labelled and (material) safety data sheets ((m)SDS) are prepared for those chemicals. These include:

- the (m)SDS for the chemical, or products and mixtures containing the chemical, must contain accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of a chemical, as well as instructions on the safe storage, handling, use and disposal of the chemical (a

review of physical hazards of the chemical has not been undertaken as part of this assessment); and
- a copy of the (m)SDS must be easily accessible to employees.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals to meet duties under the WHS Regulations are provided in the *Preparation of Safety Data Sheets for Hazardous Chemicals—Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively.

To comply with the WHS legislation, a person conducting a business or undertaking (PCBU) at a workplace must manage risks arising from storage, handling and use of a hazardous chemical. Other duties may apply to a PCBU involved in the storage, handling and use of hazardous chemicals at a workplace. Refer to the WHS legislation in the relevant jurisdiction for further information.

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

It is recommended that a PCBU should ensure that:
- equipment be designed, constructed, and operated so that, the person handling the chemical does not come into contact with the chemical and is not exposed to a concentration of the chemical that is greater than the workplace exposure standard for the chemical; and
- equipment used to handle the chemical retains the chemical, without leakage, at all temperatures and pressures for which the equipment is intended to be used and dispenses or applies the substance, without leakage, at a rate and in a manner for which the equipment is designed.

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