Ammonium fluoride ((NH4)F): Human health tier II assessment

25 November 2016

CAS Number: 12125-01-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

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.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	neutral ammonium fluoride
Structural Formula	
Molecular Formula	FH4N
Molecular Weight (g/mol)	37.04
Appearance and Odour (where available)	white odourless crystals or powder
SMILES	N{+}.F{-}

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

The National Pollutant Inventory (NPI) holds data for sources of emissions for 'Fluoride compounds' in Australia.

The following non-industrial uses have been identified in Australia:

- various salts of fluoride are listed as ingredients in medicines registered by the Therapeutic Goods Administration (TGA).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Household Products Database; and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic uses in autocare products, cleaning and washing agents.

The chemical has reported commercial uses:

- in building materials;
- for etching and frosting glass;
- as an antiseptic in brewing beer;
- to preserve wood;
- in printing/dyeing textiles; and
- in semiconductors.

The chemical has reported site-limited use as a surface treatment (for metal and non-metal surfaces), and as an intermediate in manufacturing.

The chemical has reported non-industrial uses as an antiplaque agent and in oral care products.

Restrictions

Australian

The chemical is covered by the general entry for 'FLUORIDES' in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2016), which is listed in Schedules 6, 5, 4, 3 and 2.

Schedule 6:

'FLUORIDES **except**:

a) when included in Schedule 5;

b) in preparations for human use; or

c) in preparations containing 15 mg/kg or less of fluoride ion.'

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2016).

Schedule 5:

'FLUORIDES in preparations containing 3 per cent or less of fluoride ion **except**:

a) in preparations for human use; or

b) in preparations containing 15 mg/kg or less of fluoride ion.'

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2016).

'FLUORIDES for human use', 'FLUORIDES for human topical use' and 'FLUORIDES in preparations for human use' are listed in Schedules 2, 3 and 4, respectively, of the SUSMP.

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 344/2013 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down;
- New Zealand Cosmetic Products Group Standard Schedule 5—Components cosmetic products must not contain except subject to the restrictions and conditions laid down; and
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.

In the EU, the maximum concentration permitted in ready for use oral product preparations is 0.15 % calculated as fluoride ion. When mixed with other fluorine compounds, the total fluoride ion concentration must not exceed 0.15 %. Labelling requirements also apply (Galleria Chemica, CosIng). Similar

restrictions apply in New Zealand and the ASEAN (Galleria Chemica).

Fluoride containing substances are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist') (Galleria Chemica). They are not permitted in oral products.

Existing Work 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):

- T; R23/24/25 (acute toxicity)

Exposure Standards

Australian

No specific exposure standards are available for the chemical.

Fluorides (as F) has an exposure standard of 2.5 mg/m^3 time weighted average (TWA).

International

The following exposure standards are identified for inorganic fluorides (as F)(Galleria Chemica):

- an exposure limit of 0.5–2.5 mg/m^3 TWA in different countries such as Bulgaria, Canada (Alberta, British Columbia, Saskatchewan, Yukon), Chile, China, Denmark, Egypt, France, Germany, Hungary, India, Indonesia, Ireland, Latvia, Malaysia, Malta, Mexico, Norway, Philippines, Singapore, South Africa, Sweden, Thailand, Turkey, the United Kingdom and the United States of America (USA) (Hawaii, Minnesota, Tennessee, Washington); and
- a short-term exposure limit (STEL) of 2–10 mg/m^3 in different countries such as Canada (Saskatchewan, Yukon), Hungary, Netherlands, and the USA (Washington).

Health Hazard Information

Since the chemical is composed of an ammonium cation and a fluoride anion, it will display toxicity characteristics consistent with both ions. The systemic toxicity associated with the chemical is expected to arise from the fluoride anion, whereas local effects are expected to arise from the interaction of both ions. Fluoride is considered to be an essential ion, especially in the maintenance of healthy teeth. However, it has a narrow biological range and excessive intake can have detrimental effects (e.g. dental fluorosis) (IPCS, 2002; NRC, 2006). Ammonium is a physiological component of the body and homeostatic mechanisms exist to regulate its levels. It has also been identified in chemicals that are considered of low concern to human health (NICNAS).

When data specific to the chemical being assessed are not available, health hazard information for other fluoride or ammonium compounds, such as sodium fluoride (CAS No. 7681-49-4) and ammonium chloride (CAS No. 12125-02-9; NICNASa), has been included in this report. Information on bifluorides (NICNASb) and hydrofluoric acid (NICNAS, 2001) are also relevant for this chemical (see **Toxicokinetics** below).

Toxicokinetics

The chemical can convert to the more stable ammonium bifluoride (CAS No. 1341-49-7) via ammonia loss; it is also considered to be fluoride-liberating (HSDBa). In combination with water, the chemical can release hydrofluoric acid (CDC, 2005). No other data are available for the chemical.

Following oral exposure, fluoride compounds are absorbed rapidly from the gastrointestinal tract (stomach and small intestine) by passive diffusion and absorption is almost complete (approximately 97 %) for soluble compounds. The toxicity of fluoride compounds increases with increasing solubility. Fluorides can also be absorbed from the lungs and skin. Fluoride is distributed throughout the body, detected in all organs examined, and concentrated in the skeleton and teeth (accounting for approximately 60 % of total intake in adults and 80–90 % in children). Fluoride that is not retained is excreted rapidly via the urine, and to a lesser extent via sweat and faeces (IPCS, 2002; HSDBa; HSDBb; HSDBc).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Toxic if swallowed' (T; R25) in the HSIS (Safe Work Australia). Although the available results for the chemical are not definitive, when considered with data for the related fluoride chemicals, this classification is supported.

Reported oral median lethal dose (LD50) values were (HSDBb; NICNASb; REACHa; REACHb; REACHc):

- 200<LD50<2000 mg/kg bw in Sprague Dawley (SD) rats exposed to ammonium fluoride;
- 130 mg/kg bw in SD rats exposed to ammonium bifluoride; and
- 98 mg/kg bw in male Swiss mice, 114 mg/kg bw in male white Rochester rats, and 149–223 mg/kg bw in SD rats exposed to sodium fluoride.

Reported signs of toxicity included hunching, lethargy, salivation, decreased respiratory rate, respiratory sounds and piloerection.

Dermal

The chemical is classified as hazardous with the risk phrase 'Toxic in contact with skin' (T; R24) in the HSIS (Safe Work Australia). Although there are no specific data for the chemical, the available information on the effect of fluoride in humans (see **Observation in humans** below) supports this classification.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic by inhalation' (T; R23) in the HSIS (Safe Work Australia). Although there are no specific data for the chemical, the available data on the related fluoride chemical, sodium fluoride, and information regarding the effect of fluoride in humans (see **Observation in humans** below) support this classification.

The median lethal concentration (LC50) of sodium fluoride was reported to be 1 mg/L in rats exposed to the chemical in air for four hours. Reported signs of toxicity included reduced activity, piloerection, abnormal posture, abnormal respiration, anogenital and facial staining, and nasal and ocular discharge (REACHa).

Observation in humans

Following oral exposure, fluoride can produce nausea, vomiting, abdominal pain, diarrhoea, fatigue, drowsiness, coma, convulsions, cardiac arrest and death. Some of these symptoms may be attributable to the formation of hydrofluoric acid (which is corrosive) in the stomach. A single dose of 5 mg/kg bw fluoride has been associated with adverse health effects and the lethal dose for sodium fluoride has been estimated to be 5–10 g (IPCS, 2002).

Fluoride-containing compounds are known to cause serious systemic toxicity in humans following dermal exposure, due to fluoride-associated cell death and/or chemical burns to the skin. This can result in increased levels of systemic fluoride exposure, leading to adverse health effects similar to those associated with oral exposure, such as respiratory effects, cardiac arrest and death. Exposure to fluoride-containing products on only small areas of the body surface (more than 1 % of the body surface for products containing high fluoride concentrations, and more than 5 % for products containing low fluoride concentrations) can produce these adverse effects (IPCS, 2002; IPCS, 1984; HSDBa).

The mechanism of action of the adverse health effects associated with high doses of fluoride compounds is related to complexation of calcium and magnesium following fluoride absorption. This can result in cell death due to low levels of cellular calcium, whereas the systemic effects of reduced serum calcium and magnesium levels can lead to metabolic and respiratory acidosis. Fluoride may also increase the level of serum potassium. These changes can contribute to cardiac arrhythmia and possible failure, respiratory stimulation followed by depression and possible paralysis, central nervous system depression, muscle spasms, convulsions and death (HSDBa).

Corrosion / Irritation

Corrosivity

No data are available for the chemical. The chemical is considered to be a source of ammonium bifluoride and hydrofluoric acid (CDC, 2005; HSDBa), both of which are corrosive (NICNAS, 2001; NICNASb). The ammonium cation is somewhat acidic and small amounts of these acidic species are expected to be present in ammonium fluoride solutions. Similar effects are seen for ammonium chloride, which is irritating to skin (NICNASa). Altogether, this warrants hazard classification for this chemical also (see **Recommendation** section).

The reported effects of elemental fluorine or fluoride compounds (e.g. high concentrations of sodium fluoride in industrial products) also support this. Fluoride compounds can cause delayed pain following dermal exposure, and ultimately cell death and/or chemical burns to skin. Dermal exposure may result in secondary systemic toxicity in humans. Increased levels of systemic fluoride arising from destruction of the skin barrier may then lead to the same adverse health effects as those associated with oral exposure. Exposure to small areas of the body surface (more than 1 % of the body surface

for products containing high fluoride concentrations, and more than 5 % for products containing low fluoride concentrations) can produce these adverse effects. Fluoride compounds are also reported to cause irritation and burns to the eye, as well as respiratory tract (nose and throat) irritation and direct lung injury (IPCS, 2002; IPCS, 1984; HSDBa).

Sensitisation

Skin Sensitisation

No data are available for the chemical. Based on the available data for related chemicals, the chemical is not expected to have skin sensitisation potential.

Sodium fluoride, ammonium chloride, bifluorides and hydrofluoric acid are not skin sensitisers based on the negative results in guinea pig maximisation tests or Buehler assays, or due to an expected lack of protein binding (NICNAS, 2001; NICNASa; NICNASb; REACHc).

Repeated Dose Toxicity

Oral

No data are available for the chemical. At doses much higher than those normally found in drinking water (e.g. high concentrations used in industrial processes), based on the available data in humans (see **Observation in humans** below), and data for the related chemical sodium fluoride in rodents (mice only), the chemical is expected to cause serious health effects related to skeletal fluorosis, warranting hazard classification (see **Recommendation** section).

In a repeated dose oral toxicity study, Fischer (F344/N) rats (n = 10/sex/dose) were exposed to sodium fluoride in drinking water at 0, 10, 30, 100 or 300 ppm daily for 26 weeks. Based on water intake in the two year carcinogenicity study conducted as part of this series of experiments, these doses are equivalent to approximately 0.2, 0.3, 0.8, 2.6 and 8.2 mg fluoride/kg bw/day, respectively. In male and female rats exposed at 300 ppm, body weight was significantly reduced by 17 % and 10 %, respectively. This was associated with reduced food intake of 13 % and 18 % in males and females, respectively. Signs of dental fluorosis were observed in all rats exposed at 300 ppm from the sixth week of study onwards, and this was associated with incisor tooth enamel degeneration (dysplasia) in male rats (5/6) at the end of the study. At 300 ppm, glandular stomach hyperplasia (focal to diffuse) and individual cell necrosis were observed in all male rats and 9/10 female rats; at 100 ppm, glandular stomach hyperplasia was observed in 5/10 males and 2/10 females (NTP, 1990). The effects in the stomach are considered to be local effects due to the corrosive properties of the chemical under the acidic conditions of the stomach. Therefore, a no observed adverse effect level (NOAEL) of 100 ppm (approximately 2.6 mg fluoride/kg bw/day) can be determined based on the dental fluorosis observed at ≥300 ppm (approximately 8.2 mg fluoride/kg bw/day). In humans, dental fluorosis is considered to be a pathological effect with minimal biological consequences for adults.

In a repeated dose oral toxicity study, B6C3F1 mice (n = 8–12/sex/dose) were exposed to sodium fluoride in drinking water at 0, 10, 50, 100, 200, 300 or 600 ppm daily for 26 weeks. Based on water intake in the two year carcinogenicity study conducted as part of this series of experiments, these doses are equivalent to approximately 0.6, 0.6, 2.8, 5.3, 11.3, 16.9 and 33.9 mg fluoride/kg bw/day, respectively. Deaths prior to study termination were recorded in 1/8 and 4/9 male mice exposed at 300 and 600 ppm, respectively; and in 9/11 female mice exposed at 600 ppm. Early deaths were associated with acute nephrosis, myocardial degeneration and liver cell enlargement. Body weight gain was significantly reduced in male mice exposed at ≥200 ppm, and in female mice exposed at 200 and 300 ppm. Reduced body weight gain was also observed in females exposed to 600 ppm, but this was not statistically significant due to the low number of mice alive in this group at termination. There was a statistically significant dose-related increase in bone and urine fluoride content with increasing drinking water fluoride concentration. Incisor tooth enamel degeneration (dysplasia) was observed in 1/5, 5/5 and 1/1 male mice exposed at 100, 300 and 600 ppm, respectively; and in 1/2, 1/5, 1/3 and 2/2 female mice exposed at 0, 200, 300 and 600 ppm, respectively. Lesions (increased osteoid or hypomineralisation) in the femur and tibia were observed in males exposed at ≥50 ppm and in females exposed at ≥100 ppm (NTP, 1990). The lowest observed adverse effect level (LOAEL) was determined to be 50 ppm (approximately 2.8 mg fluoride/kg bw/day), based on the bone lesions observed at all levels of exposure.

In another repeated dose oral toxicity study (similar to OECD TG 407), SD rats (n = 10/sex/dose) were administered sodium fluoride at 0, 0.0025, 0.025 or 0.25 w/w % in water (equivalent to 0, 0.25, 2.5 and 25 mg/kg bw/day, respectively) once per day for 28 days by gavage. An NOAEL of 0.025 % w/w (2.5 mg/kg bw/day) was reported based on significantly reduced mean cell haemoglobin values; significantly reduced circulating total protein; significantly increased absolute stomach weight; significantly increased urinary fluoride; significantly increased tooth fluoride content; and altered mineral content in femur bones (significantly increased zinc and fluoride) in all rats at the highest dose (REACHc).

In a combined chronic toxicity/carcinogenicity study (similar to EPA OPP 83-5), SD rats (n = 70/sex/dose) were exposed to sodium fluoride at 0, 4, 10 and 25 mg/kg bw/day via the diet for up to 99 weeks. An NOAEL of 4 mg/kg bw/day can be determined, based on skeletal fluorosis in the skull of rats at doses ≥10 mg/kg bw/day, which increased in incidence and severity with increasing dose and duration of exposure. Other effects included dental fluorosis (malformed incisors, enamel hypoplasia) observed at doses ≥4 mg/kg bw/day from 26 weeks onwards; and thickening of the non-glandular stomach, as well as chronic inflammation of the gastric mucosa at doses ≥4 mg/kg bw/day (REACHc).

Dermal

No data are available for the chemical or the related chemicals. All REACH dossiers indicate 'data waiving' (a reason for not providing the information) based on 'exposure considerations' or 'other justification' for some of the related chemicals (REACHa; REACHc; REACHd).

Inhalation

Only one study, with limited relevance, is available for the chemical. No other data are available for the chemical or the related chemicals. All REACH dossiers indicate data waiving for 'exposure considerations' or 'other justification' for some of the related chemicals (REACHa; REACHc; REACHd).

In male Wistar rats exposed to the chemical in air at a concentration equivalent to the mean annual limit of fluoride compounds (not specified), the composition and metabolic activity of liver microsomal fractions were investigated at three, six and nine months. After three months' exposure, microsomal protein content was increased, whereas phospholipid content was decreased. After six months' exposure, microsomal cholesterol was elevated. After nine months' exposure, there were no changes in cytochrome P450 and cytochrome b5 activity, whereas activity of cytochrome c reductase was decreased. Substrate metabolism was also affected, with aniline turnover inhibited after six months' and aminopyrine turnover inhibited after nine months' exposure to the chemical. It was concluded that exposure to the chemical could contribute to impaired detoxification by the liver (HSDBa).

Observation in humans

Occupational exposure to fluoride-containing chemicals can cause skeletal fluorosis, a condition that results in brittle bones and susceptibility to fractures in the long term. When occupational exposure limits to fluoride are exceeded or with increasing duration of employment, skeletal effects such as joint pain, initial increased bone density and osteosclerosis have been reported in workers (IPCS, 1984; IPCS, 2002).

Based on evidence from epidemiological studies in Indian and Chinese populations with high long-term (environmental) exposure to fluoride, it has been suggested that intake of 6 mg fluoride/day is associated with increased risk of bone effects and that intake of 14 mg fluoride/day is highly associated with increased bone fracture risk (IPCS, 2002). This equates to a dose of approximately 0.09–0.2 mg/kg bw/day for a 70 kg person.

Genotoxicity

No data are available for the chemical. Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies for related chemicals, the chemical is not expected to be genotoxic.

Ammonium chloride, bifluorides and hydrogen fluoride (NICNAS, 2001; NICNASa; NICNASb) are not considered to be genotoxic.

For sodium fluoride, while there are mostly positive in vitro results in mammalian cell assays, there are also many conflicting in vivo results for various assays. Genotoxicity is not expected to occur in humans based on the anticipated pattern (route, duration, level) of exposure to the chemical (IPCS, 1984; NTP, 1990; IPCS, 2002; ATSDR, 2003).

Carcinogenicity

No data are available for the chemical. Based on the available data in humans, and data for the related chemical sodium fluoride in rodents, the chemical is not expected to be carcinogenic.

The International Agency for Research on Cancer (IARC) has classified 'Fluorides (inorganic, used in drinking water)' as 'not classifiable as to their carcinogenicity to humans', based on inadequate evidence for carcinogenicity to humans from water fluoridation and cancer studies, and inadequate evidence for carcinogenicity to animals exposed to sodium fluoride (IARC, 1987).

Most epidemiological studies examining water fluoridation and cancer have not identified increased cancer mortality or increased site-specific cancer incidence in humans. Two studies have identified a link between water fluoridation and cancer, but the interpretation of these studies is limited due to confounding experimental factors (ATSDR, 2003).

In carcinogenicity studies using F344/N rats (n = 70–100/sex/dose) and B6C3F1 mice (n = 70–100/sex/dose), animals were exposed to sodium fluoride at 0, 25, 100 or 175 ppm in drinking water daily for 103 weeks. This is equivalent to 0, 11, 45 and 79 ppm of fluoride ion or doses of approximately 0.2, 0.8, 2.6 and 4.3 mg fluoride/kg bw/day for rats and 0.6, 1.8, 5.3 and 8.6 mg fluoride/kg bw/day for mice. There was no evidence of carcinogenicity in female F344/N rats and in B6C3F1 mice. There was equivocal evidence of carcinogenicity in male F344/N rats, based on marginal increases in osteosarcoma in animals exposed to sodium fluoride at ≥100 ppm (0/80, 0/51, 1/50 and 3/80 at 0, 25, 100 and 175 ppm, respectively) (NTP, 1990).

In a combined chronic toxicity/carcinogenicity study (similar to EPA OPP 83-5), SD rats (n = 70/sex/dose) were exposed to sodium fluoride at 0, 4, 10 and 25 mg/kg bw/day via the diet for up to 99 weeks. There were no pre-neoplastic or neoplastic changes associated with treatment (REACHc).

In other carcinogenicity studies using Swiss CD1 mice or DBA mice exposed to sodium fluoride in the drinking water or via the diet, tumours were observed in treated mice at rates equivalent to those seen in the control group of mice (IARC, 1982).

Reproductive and Developmental Toxicity

No data are available for the chemical. Based on the available data for related chemicals, the chemical is not expected to cause reproductive and developmental toxicity.

Sodium fluoride, ammonium chloride, and hydrofluoric acid are not considered to cause reproductive and developmental toxicity (NICNAS, 2001; NICNASa; REACHc).

Other Health Effects

Neurotoxicity

Based on a comprehensive literature review of rodent studies examining learning and memory, a conclusion on the impact of fluoride-containing chemicals on this aspect of neurobehaviour can not be made (NTP, 2016). Although fluoride-containing compounds have been shown (by histological, biochemical and molecular approaches) to affect brain function directly or indirectly, additional research is required to assist in determining if there are neurotoxic or neurobehavioural effects associated with excess fluoride exposure (NRC, 2006).

In Australia, the target fluoride concentration in fluoridated water is 0.7–1.0 mg/L (equivalent to 0.7–1.0 ppm) (NHMRC, 2011). Human evidence suggests that consumption of fluoride in water greater than the recommended fluoridation level (0.7–1.2 ppm) is associated with lower IQ in children. The confidence in this evidence is considered 'limited, primarily due to poor reporting quality, lack of consideration of confounding (e.g., nutritional status, socioeconomic status, iodine deficiency), and concern for co-exposures to relatively high levels of other known neurotoxicants such as lead or arsenic'. Available animal studies were analysed to determine if this would aid in interpreting the human data. Overall, the animal evidence was considered low-to-moderate confidence for an effect on learning and memory, being weaker in rodents exposed during development and strongest in rodents exposed as adults. It was concluded that additional research is needed and that the NTP was conducting studies to fill in the identified data gaps (NTP, 2016).

Endocrine Disruption

Based on evidence in humans and animals, fluoride can affect normal endocrine function and responsiveness, but further research is required to characterise these effects. In humans, the main endocrine effects reported included impacts on thyroid function (due to altered thyroxine (T4) and triiodothyronine (T3) concentrations), elevated thyroid stimulating hormone (TSH), increased calcitonin activity, impaired glucose tolerance and impacts on sexual maturity timing (NRC, 2006).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (toxic effects following a single exposure through the oral, dermal and inhalation routes) and local effects (corrosivity).

The chemical can also cause long-term effects following repeated high level (e.g. industrial) exposure.

Public Risk Characterisation

The chemical is covered by the general entry for 'FLUORIDES' listed on Schedules 2, 3, 4, 5, 6 of the SUSMP (SUSMP, 2016). As the current controls are considered adequate to minimise the risk to public health posed by cosmetic and domestic products containing the chemical, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while 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 and local health effects, and the long-term effects following repeated high level exposure, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling 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

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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 physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Toxic in contact with skin (T; R24)* Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1 (H314)
Repeat Dose Toxicity	Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)

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

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] 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 oral, dermal, ocular 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 depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- 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 help meet 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.

References

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