Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Compounds of dimethyltin

Evaluation statement

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AICIS evaluation statement

Subject of the evaluation

Compounds of dimethyltin

Chemicals in this evaluation

Name	CAS registry number
Stannane, bis(dodecylthio)dimethyl-	51287-84-4
9-Octadecenoic acid, 2-mercaptoethyl ester, (Z)-, reaction products with dichlorodimethylstannane, sodium sulfide (Na_2S) and trichloromethylstannane	68442-12-6

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

The chemicals are a group of dimethyltin compounds listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of these chemicals.

These chemicals have been assessed as a group because the toxicity of organotin compounds depends largely on the organotin moiety, and these chemicals are structurally similar. Based on a review of the available information, dimethyltin compounds have been reported to cause reproductive, neurodevelopmental, nervous system and immune system toxicity. These human health effects are likely to be the main drivers of any risk management recommendations for this group of chemicals. The toxicity of the unknown variable composition or biological substance (UVCB) CAS No. 68442-12-6 will be influenced by the relative proportion of dimethyltin and monomethyltin substances. Monomethyltin-based substances have been found to be less toxic (NICNAS 2018a).

Although data for local effects are presented for chemicals where available, this evaluation will not provide conclusions on these endpoints where data are not available.

In this evaluation, CAS No. 51287-84-4 will be referred to as dimethyltin bis(dodecylmercaptide) and CAS No. 68442-12-6 as the UVCB substance.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the use or volume of use of these chemicals in Australia. Data on emissions and sources of emissions for organotin compounds in Australia indicate site limited use in polymer product manufacturing.

Based on international information, dimethyltin compounds are used for rigid PVC processing applications, from PVC pipe, pipe fittings, and clear bottles to rigid film and sheet, cellular PVC, vinyl siding and window profile extrusions. The UVCB substance is used as a heat stabiliser in the processing of PVC pipes (unpublished information 2022).

Human health

Summary of health hazards

There is limited toxicological information for the chemicals in this group. The main driver for the toxicity of dimethyltin compounds is expected to be the dimethyltin moiety. Although the levels at which effects are observed may vary for different dimethyltin compounds, similar effects and target organs were observed across the suite of studies, supporting the view of a similar mechanism of toxicity. Therefore, available data for the UVCB substance and other dimethyltin compounds, including dimethyltin dichloride (DMTC) and dimethyltin mercaptoacetate compounds, are used to draw conclusions regarding the systemic effects of chemicals in this group. Th latter 2 compounds were assessed previously and their reports should be read in conjunction with this evaluation statement (NICNAS 2018b; NICNAS 2018c).

Based on the weight of evidence, the critical health effects for risk characterisation are adverse systemic long term effects on:

- reproduction
- neurodevelopment
- the immune system
- the nervous system.

Repeated exposure to the UVCB substance in rats led to decreased thymus weight and increased kidney weights in both sexes with dose-related changes in the bladder. One study found that the chemical did not cause significant adverse effects up to a dose of 90 mg/kg bw/day and the second one found signs of nephrotoxicity at 9 mg/kg bw/day and a decrease in thymus weight and marked increase in kidney weight at 135 mg/kg bw/day in both sexes. Although effects were seen at higher doses in the repeated dose studies of the UVCB substance compared with other dimethyltin compounds, this may be related to the high percentage of monomethyltin species in this particular UVCB. Exposure to DMTC has been linked to decreased thymus weights in males, thymus atrophy in both sexes and increased kidney weights in females with histopathological changes in the thymus, brain and kidneys in both sexes. Neurotoxic effects were noted with signs including convulsions and tremors. Histopathological changes included neuronal necrosis, ventricular dilation, and white matter vacuolisation in the brain and spinal cords (NICNAS 2018b). Neuronal necrosis has also been observed in a 90 day study with dimethyltin bis(2-ethylhexyl mercaptoacetate) (DMT(2-EHMA)) with effects observed at doses of approximately 15 mg/kg bw/day.

The available data on reproductive toxicity for DMTC indicated the presence of foetal variations and malformations, and developmental neurotoxicity at low doses in some of the animal studies (NICNAS 2018b). A recent prenatal developmental toxicity study with DMT(2-EHMA) in rats found no effects but toxicity at higher doses could not be ruled out (unpublished data, 2022).

The chemicals are not considered to be genotoxic based on the available data for the UVCB substance (unpublished data, 2022), DMTC (NICNAS 2018b) and DMT(2-EHMA) (NICNAS 2018c), Carcinogenicity was not observed in long term studies using mixtures of mono- and dimethyltin compounds (WHO 2006).

Based on limited information for dimethyltin bis(dodecylmercaptide) and read across data from dimethyltin mercaptoacetate compounds, the chemicals may have low to moderate acute oral and inhalation toxicity and low acute dermal toxicity.

Experimental, read across and in silico data indicate that the chemicals in this group are not expected to be irritating to the skin or eyes. This is supported by QSAR modelling for dimethyltin bis(dodecylmercaptide).

There are no data on skin sensitisation. Although dimethyltin dimercaptoacetate compounds are skin sensitisers (NICNAS 2018c), the anionic ligand may contribute to this effect. No structural alerts for protein binding based on the mechanistic profiling functionality were found for dimethyltin bis(dodecylmercaptide) using OECD QSAR Toolbox v4.2.

Toxicokinetic data for a compound related to those in this evaluation showed less hydrolysis to simple dimethyltin species compared with results for other dimethyltin substances, and this may lead to lower overall toxicity. However repeat dose toxicity studies found effects, albeit at higher doses, related to those seen for other dimethyltin substances. Accordingly, it is not possible to completely dismiss the possibility that some simple dimethyltin species are produced, with consequent toxicity outcomes, such as reproductive toxicity.

Health hazard classification

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety. This evaluation does not consider classification of physical and environmental hazards. These recommended classifications are based on read across principles (see **Supporting Information – Grouping Rationale** section). If empirical data become available for either member of the group indicating that a lower (or higher) classification is appropriate for a specific chemical, this data may be used to amend the default classification for that chemical. The toxicity of the UVCB substance will vary depending upon the relative amounts of dimethyltin and monomethyltin compounds, with UVCBs containing high percentages of monomethyltin being expected to be less toxic.

Health hazards	Hazard category	Hazard statement
Specific target organ toxicity - repeated dose exposure	STOT Rep. Exp. 2	H371: May cause damage to the nervous system and immune system through prolonged or repeated exposure
Reproductive toxicity	Repr. 2	H361d: Suspected of damaging the unborn child

Summary of health risk

Public

These chemicals are currently listed on in the Poisons Standard–the Standard for the Uniform Scheduling of Medicines and Poisons (the SUSMP)**,** Schedule 7 for tin organic compounds. At concentrations greater than 1%, these chemicals are not available to the general public. A number of warning statements, first aid instructions and safety directions relating to tin organic compounds may apply (TGA 2021).

Based on the available use information, the public may be exposed to the chemicals at very low concentrations in articles through their use in the manufacture of plastics and potential use in food contact applications.

Internationally, a group tolerable daily intake (TDI) of (0.1 µg/kg bw as Sn) for organotin compounds in foodstuffs, based on systemic effects, has been established (European Commission 2009).

To reduce the identified risk of organotin compounds transferred from food packaging to foodstuffs, the overall exposure should be lower than the TDI. The dominant contribution to human intake of organotin compounds (mainly tributyltin) is via consumption of fish. Exposure to other organotin compounds, including these chemicals, is expected to be generally low both from food contact and handling plastic articles.

Based on the available use information, there are no identified risks to the public that require further risk management.

Workers

During product formulation and packaging, dermal and inhalation exposure might 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. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical systemic long term health effects, these chemicals could pose a risk to workers.

Control measures to minimise dermal exposure and inhalation exposure (if aerosolised) are needed to manage the risk to workers (see **Proposed means for managing any risks** section).

Control measures implemented due to the reprotoxicity and repeated dose classifications are expected to be sufficient to protect workers from any potential sensitisation health effects.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from dermal and inhalation exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals if valid techniques are available to monitor the effect on the worker's health
- conducting air monitoring to ensure control measures in place continue to work effectively.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this evaluation statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

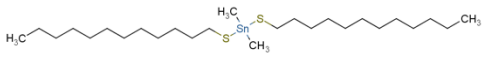
Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

Supporting information

Grouping rationale

This group of chemicals consists of dimethyltin bis(dodecylmercaptide) and a UVCB substance. Both compounds are expected to release dimethyltin compounds following metabolism, although toxicokinetic data is limited to one in chemico hydrolysis study for the former chemical. Di-substituted organotin compounds have the general formula R_2SnX_2. The toxicity of organotin compounds depends largely on the organotin moiety (R group), with the anionic ligand (X) mostly influencing physicochemical properties and local toxicity. Although the levels at which effects are observed may vary for different dimethyltin compounds, similar effects and target organs were seen across the suite of studies, supporting the view that a similar mechanism of toxicity is operating. The UVCB substance may also release monomethyltin compounds. However, the toxicity of monoalkyltin compounds is lower than that of the related dialkyltin compounds (NICNAS 2018a).

Chemical identity

Chemical name	Stannane, bis(dodecylthio)dimethyl-
CAS No.	51287-84-4
Synonyms	dimethyltin bis[n-dodecylmercaptide] dimethyltin bis(lauryl mercaptide)
Structural formula	
Molecular formula	C26H56S2Sn
Molecular weight (g/mol)	551.57
SMILES	S(CCCCCCCCCCCC)[Sn](SCCCCCCCCCCCC)(C)C
Chemical description	Organometallic compound

Chemical name	9-Octadecenoic acid, 2-mercaptoethyl ester, (Z)-, reaction products with dichlorodimethylstannane, sodium sulfide (Na_2S) and trichloromethylstannane
CAS No.	68442-12-6
Synonyms	-
Structural formula	No structure available
Molecular formula	Not specified

Molecular weight (g/mol)	Not specified
SMILES	-
Chemical description	Organometallic compound and UVCB

Relevant physical and chemical properties

Dimethyltin bis(dodecylmercaptide) is an extremely pale liquid with the following properties:

- boiling point (predicted) 532.2±33.0 °C at 760 Torr (mmHg)
- vapour pressure (predicted) 0.0 +/- 1.4 mm Hg at 25ºC
- density (experimental) 1.08 g/cm^3.

Based on the predicted vapour pressure, this chemical has low volatility.

There is no information on the physical or chemical properties for the UVCB substance.

Introduction and use

Australia

No specific information is available regarding the introduction, import and use of these chemicals in Australia.

The National Pollutant Inventory (NPI) provides information on emission sources of organotin compounds in Australia. The following site limited sources were identified by the NPI in 2019/2020:

- glass and glass product manufacturing
- polymer product manufacturing.

Information provided through public comment stated that dimethyltin compounds are not used in glass or glass product manufacturing (unpublished information, 2022).

International

In general, dimethyltin compounds are used in site-limited applications for processing rigid PVC.

The following international uses for dimethyltin bis(dodecylmercaptide) have been identified through the:

- European Union Registration, Evaluation and Authorisation of Chemicals (REACH)
- Substances in Preparations in Nordic countries (SPIN) database.

Based on international use information, the chemical is reported to be used in site limited applications as a catalyst, process regulator and heat stabiliser in the manufacture of plastic products. It is also used for the manufacture of textile, leather or fur, wood and wood

products, pulp, paper and paper products, chemicals, rubber products, fabricated metal products, electrical, electronic and optical equipment, machinery and vehicles and furniture.

These products may have a number of commercial applications including:

- adhesives and sealants
- insulating materials
- construction materials
- coating products
- metal surface treatment products
- non-metal-surface treatment products
- paper chemicals
- textile treatment products and dyes.

Some of these commercial uses may also be used in domestic applications. No consumer uses are registered under REACH and the SPIN database suggests that the registered product uses do not indicate direct exposure to consumers.

The UVCB substance is used as a heat stabiliser (unpublished information, 2022).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

Tin organic compounds are listed in the Poisons Standard—SUSMP in Schedule 7 (TGA, 2021). This entry covers the chemicals in this group.

"TIN ORGANIC COMPOUNDS, being dialkyl, trialkyl and triphenyl tin compounds where the alkyl group is methyl, ethyl, propyl or butyl except:

a) when separately specified in this Schedule;

b) in plastics;

c) in semi-solid sealants, adhesives or elastomers containing 1% or less of the dialkyl, trialkyl or triphenyl tin component; or

d) in paint containing 1% or less of such compounds calculated as tin in the non-volatile content of the paint."

Schedule 7 chemicals are described as: 'Dangerous poisons – Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.' (TGA 2021).

Workers

Tin and its compounds are listed in the Work Health and Safety Regulations (2021 revision) as restricted hazardous chemicals—the restricted use is 'abrasive blasting at a concentration of greater than 0.1% as tin' (SWA 2021).

These chemicals are not specifically listed as hazardous chemicals on the Hazardous Chemicals Information system (HCIS) (SWA).

Tin organic compounds (as Sn) have an exposure standard of 0.1 mg/m^3 time weighted average (TWA) and 0.2 mg/m^3 short term exposure limit (STEL) (SWA).

In 2020, Safe Work Australia reviewed and recommended retaining the TWA. The recommended TWA is considered protective for effects on the central nervous system and other systems. A STEL was not recommended due to insufficient data relating to acute exposures (SWA 2020). At the time of publication of this evaluation statement, these workplace exposure standards were yet to be finalised.

International regulatory status

Exposure standards

The following exposure standards were identified for tin, organic compounds (as Sn) (Chemwatch):

An exposure limit of 0.1 mg/m^3 TWA and 0.2–0.4 mg/m^3 STEL in different countries such as Bulgaria, Canada (Alberta, British Columbia, Ontario, Quebec, Saskatchewan, Yukon), Denmark, Egypt, Estonia, France, Greece, Malaysia, Mexico, Norway, Philippines, Singapore, South Africa, Spain, Sweden, Taiwan, the United Kingdom and the United States of American (California, Hawaii, Minnesota, Tennessee, Vermont, Washington).

European Union

Tin compounds (organic) are listed on the following (Chemwatch):

- Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles intended to come into contact with foodstuffs—Limits for finished articles; a limit of 0.05 mg/kg (as Sn) applies.

Health hazard information

Toxicokinetics

Studies have shown that in general, sulfur or carboxylate-based ligands of organotin compounds are easily displaced under mild physiological conditions (NICNAS, 2018c). Abiotic hydrolysis of dimethyltin bis(dodecylmercaptide) has been studied. However, no data are available regarding the in vivo metabolism of these chemicals.

The hydrolysis of dimethyltin bis(dodecylmercaptide) was studied using Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 111 at pH 1.2, 4, 7 and 9 using NMR spectroscopy. The chemical was reported to be hydrolytically stable at pH

4, 7 and 9. After 5 days of hydrolysis at 50 °C, less than 10% of the test material was hydrolysed (half-life at 25 °C >1 year). At simulated gastric conditions (0.1 M HCl/pH 1.2 at 37 °C/4 h) the only identifiable breakdown product was the monochloride substituted product of the test material, chlorododecylthiodimethylstannane (REACH). Similar results were found in an in vitro hydrolysis study using DMT(2-EHMA) (up to 29 % of the mono-chloro ester was formed after 72 h at the same temperature and pH) (NICNAS 2018c).

Acute toxicity

Oral

Limited data are available. Dimethyltin bis(dodecylmercaptide) has a reported median lethal dose (LD50) in rats of 8500 mg/kg bw (no study details), indicating low acute oral toxicity. Sub-lethal signs of toxicity included general depressed activity, somnolence and haemorrhage (CCOHS).

Dimethyltin alkyl mercaptoacetate compounds have moderate oral acute toxicity with LD50 values in the range 1000–1735 mg/kg bw (NICNAS 2018c).

Dermal

No data are available for these chemicals. Dimethyltin alkyl mercaptoacetate compounds have low acute dermal toxicity (NICNAS 2018c).

Inhalation

Based on the limited data, dimethyltin bis(dodecylmercaptide) has moderate acute inhalation toxicity. A low median lethal concentration (LC50) in rats of 3.3 mg/L was reported with no study details. Sub-lethal signs of toxicity included unspecified effects on the lungs and thorax in addition to haemorrhage (CCOHS).

Dimethyltin alkyl mercaptoacetate compounds have low acute inhalation toxicity (NICNAS 2018c).

Given the limited study details for the LC50 value, classification is not warranted.

Corrosion/Irritation

Skin irritation

Based on two in vitro studies, dimethyltin bis(dodecylmercaptide) is not expected to be irritating to the skin.

In a GLP compliant in vitro skin corrosion assay conducted in accordance with OECD TG 431, the chemical was applied to reconstructed human epidermis (EpiDerm human skin model) for 3 and 60 minutes. The mean tissue viability was 80.9 % and 82.3% after 3 and 60 minutes respectively. Substances that do not reduce viability to less than 50% after 3 minutes and less than 15% after 60 minutes using this human skin model are classified as non-corrosive. Therefore, the chemical is considered to be unlikely to have the potential to cause corrosion in vivo following application to skin (REACH).

In a GLP compliant in vitro skin irritation study conducted in accordance with OECD TG 439 (in vitro reconstructed human epidermis (RHE) test method for skin irritation), the chemical was applied to RhE for an exposure period of 15 minutes followed by an observation period of 42 hours. A mean tissue viability value of 80.9% was reported for the chemical in this study, and it was determined not to be irritating to the skin (test chemicals may be considered to be non-irritating to skin if the tissue viability after exposure and post-treatment incubation is >50%). Interpretation of results obtained from OECD TG 439 studies do not allow for distinction between irritation and corrosion (REACH).

The corrosive effects observed for DMTC (NICNAS 2018b) are not expected to occur for these chemicals. Dimethyltin alkyl mercaptoacetate compounds are considered to be slight skin irritants (NICNAS 2018c).

Eye irritation

Based on one in vitro study, dimethyltin bis(dodecylmercaptide) is not expected to be irritating to eyes.

In a GLP compliant ex vivo eye corrosivity/irritation study conducted according to OECD TG 437, the chemical was applied to three bovine corneae per experiment. The mean in vitro irritancy score (IVIS) was 0.7 (IVIS >55 is regarded as serious eye damage and IVIS ≤3 is UN GHS No Category). Based on the criteria of the assay, the chemical did not meet the GHS criteria for classification (REACH).

The corrosive effects observed for DMTC (NICNAS 2018b) are not expected to occur for these chemicals. Dimethyltin alkyl mercaptoacetate compounds are considered to be slight eye irritants (NICNAS 2018c).

Repeat dose toxicity

Based on the weight of evidence, the chemicals are expected to cause serious systemic health effects following repeated exposure, which warrants hazard classification. The broadly consistent adverse effects data from repeated dose studies indicate similar modes of action across all dimethyltin compounds with different potencies, potentially resulting from different extent of hydrolysis to simple dimethyltin species following metabolism. The toxicity of the UVCB substance will vary depending upon the relative amounts of dimethyltin and monomethyltin compounds, with UVCBs containing high percentages of monomethyltin being expected to be less toxic.

Chemicals covered by evaluation

Two 90 day repeat dose studies were available for the UVCB substance. One study found that the chemical did not cause significant adverse effects up to a dose of 90 mg/kg bw/day and the second one found signs of nephrotoxicity at 9 mg/kg bw/day and a decrease in thymus weight and marked increase in kidney weight at 135 mg/kg bw/day in both sexes. The UVCBs used in both studies had high ratios of monomethyltin to dimethyltin species (unpublished data, 2022).

In a non-GLP compliant 90 day subchronic dietary study, albino rats (10/sex/dose) were administered the chemical in feed at 0, 30, 100, 300 or 1000 ppm (approximately equivalent to 0, 2.7, 9, 27 and 90 mg chemical/kg bw/day). Food intake was slightly reduced at 1000 ppm in both sexes during the first few weeks of the experiment and the specific gravity of the urine was also slightly decreased. There were no treatment-related changes in general

condition, behaviour, survival, relative organ weights (including brain, kidneys and thymus), volume of urine, haematological findings, gross and microscopical pathological examinations at any dose levels. The no observed adverse effects level (NOAEL) was determined to be 300 ppm (15 mg/kg bw/day) for the chemical (unpublished data, 2022).

In a non-GLP compliant 90 day subchronic dietary study, albino rats (10/sex/dose) were administered the chemical in feed at 0, 100, 300 or 1500 ppm (approximately equivalent to 0, 9, 27 and 135 mg chemical/kg bw/day). Growth and food intake in males and food intake in females were decreased at 1500 ppm. Small changes in haematological parameters were observed at this dose in both sexes. The following treatment-related changes were observed in the urine at 1500 ppm: increased turbidity, pH, amount of phosphate crystals and volume and a marked decrease in specific gravity. The level of tin in the kidneys, liver and femur was increased at 1500 ppm in both sexes. A slight increase in tin levels was observed in these organs at 100 and 300 ppm. The relative weight of the kidneys was markedly increased and that of the thymus was decreased at 1500 ppm in both sexes. Adrenal weight was slightly increased at 1500 ppm in males only. The changes in the relative weight of the thymus and adrenals in the high dose group were not accompanied by dose-related histological findings. Slight histopathological changes in the kidneys were found in both sexes (enlarged nuclei and foamy cytoplasm in the epithelial cells of the proximal tubules). The epithelium of the urinary bladder was found to be slightly thickened in a number of males and females of the 300 and 1500 ppm groups, and also in one male of the 100 ppm group. The NOAEL was determined to be slightly lower than 100 ppm based on the nephrotoxic findings at the lowest dose (unpublished data, 2022).

Other dimethyl tin compounds

In a 90 day repeated dose toxicity and neurotoxicity study conducted in accordance with OECD TG 408 and 424, Sprague Dawley (SD) rats (15/sex/dose) were administered DMT(2-EHMA) in diets at doses of 10, 25, 60 and 175 ppm. Neuronal necrosis characterised by cytoplasmic shrinkage with intense eosinophilia (red neuron) accompanied by karyorrhexis or karyolysis of nuclei in the piriform cortex, cornu ammonis (CA1) and dentate gyrus of the hippocampus was observed in 3 females treated with 175 ppm (approximately equivalent to 14.96 mg/kg/bw/day). No treatment related changes were noted in the neurological/functional observation battery test in all the tested dose groups. No effects in other organs including the thymus and the kidney were observed. The NOAEL was 60 ppm (approximately 5.74 mg/kg bw/day) in females and 175 ppm (14.96 mg/kg bw/day) in males (unpublished data, 2022).

Exposure to DMTC has been linked to decreased thymus weights in males, thymus atrophy in both sexes and increased kidney weights in females with histopathological changes in the thymus, brain and kidneys in both sexes. Neurotoxic effects were noted with signs including convulsions and tremors. Histopathological changes included neuronal necrosis, ventricular dilation, and white matter vacuolisation in the brain and spinal cords (NICNAS 2018b).

Genotoxicity

The chemicals are not considered to be genotoxic based on the available data for the UVCB substance (unpublished data 2022), DMTC (NICNAS 2018b) and DMT(2-EHMA) (NICNAS 2018c),

Negative results were reported for the following GLP compliant in vitro bacterial reverse mutation assays using the UVCB substance:

- two studies in *Salmonella typhimurium* TA 1535, 1537, TA98 and TA100 with and without metabolic activation at concentrations up to 5000 µg/plate.

- two studies in *Escherichia coli* strain WP2uvrA with and without metabolic activation at concentrations up to 5000 µg/plate.

In vitro and in vivo studies using DMTC showed mixed and negative results respectively (NICNAS 2018b). Negative results were reported for bacterial reverse mutation studies using DMT(2-EHMA) (NICNAS 2018c).

Reproductive and developmental toxicity

There are limited data available to evaluate the potential for this group to have reproductive or developmental adverse effects. Exposure to DMTC was associated with foetal variations and malformations, and developmental neurotoxicity at low doses in some of the animal studies (NICNAS 2018b). Although adverse effects were not observed with a recent prenatal developmental toxicity study in rats exposed to DMT(2-EHMA) (unpublished data, 2022), effects at higher doses cannot be ruled out. Thus, classification for developmental toxicity is supported based on the weight of evidence.

In a prenatal developmental toxicity study conducted according to OECD TG 414 and compliant with GLP, DMT(2-EHMA) (98 % in arachis oil) was administered by gavage to time-mated female Wistar Han rats (22/dose) at 0, 5, 10 and 25 mg/kg bw/day from day 6 to 20 post-coitum, inclusive. No treatment-related effects were noted in dams including organ weights, macroscopic evaluation, uterine contents, corpora lutea, implantation sites and pre- and post-implantation loss. No adverse developmental effects were observed in foetuses, including developmental parameters such as litter size, sex ratio, foetal body weights, anogenital distances and incidences of external, soft tissue or skeletal abnormalities. A NOAEL for developmental toxicity was reported to be at least 25 mg/kg bw/day and a maternal NOAEL was established at 10 mg/kg bw/day based on decreased food consumption and lower mean body weight gain adjusted for gravid uterus at 25 mg/kg bw/day (unpublished data 2022).

References

CCOHS (Canadian Centre for Occupational Health and Safety) (2021) *Record for CAS No. 51287-84-4*, CCOHS, accessed December 2021.

Chemwatch (n.d.) *Galleria Chemica*, Chemwatch website, accessed December 2021.

EC (European Commission) (2009). *COMMISSION STAFF WORKING DOCUMENT Impact Assessment Report Proposal for a COMMISSION DECISION amending Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions,* accessed December 2021.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2018a) *Single Assessment Report - Stannane, triichlorodimethyl-: Human Health Tier II assessment*, NICNAS, accessed December 2021.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2018b) *Single Assessment Report - Stannane, dichlorodimethyl-: Human Health Tier II assessment*, NICNAS, accessed December 2021.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2018c) *Group Assessment Report -* Dimethyltin alkyl mercaptoacetates*: Human Health Tier II assessment*, NICNAS, accessed December 2021.

NPI (National Pollutant Inventory) (n.d.) *Substance list and thresholds*, NPI website, accessed December 2021.

OECD (Organisation for Economic Co-operation and Development) (2018) *Quantitative Structure-Activity Relationship Toolbox (Version 4.2)*, Computer software, OECD, accessed December 2021.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.) *Registered dossier for CAS No. 51287-84-4,* European Chemicals Agency website, accessed December 2021.

SPIN (Substances in Preparation in Nordic Countries) (n.d.) *SPIN Database,* SPIN website, accessed December 2021.

SWA (Safe Work Australia) (n.d.) *Hazardous Chemicals Information System*, SWA website, accessed December 2021.

SWA (Safe Work Australia) (2021) *Model Health and Safety Regulations (2021),* SWA, accessed December 2021.

SWA (Safe Work Australia) (2021) Draft evaluation report workplace exposure standard tin organic compounds, SWA, accessed December 2021.

TGA (Therapeutic Goods Administration) (2021) *Standard for the Uniform Scheduling of Medicines and Poisons No. 34 (Poisons Standard October 2021)*, TGA, accessed December 2021.

UNECE (United Nations Economic Commission for Europe) (2017) *Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Seventh Revised Edition*, UNECE, accessed December 2021.

US EPA (United States Environmental Protection Agency) (2012) *Chemical Data Reporting Data*, US EPA website, accessed December 2022.

US EPA (2016) *Chemical Data Reporting Data*, US EPA website, accessed December 2022.

WHO (World Health Organization) (2006), *Concise International Chemical Assessment Document 73 (CICAD), Mono and disubstituted methyltin, butyltin, and octyltin compounds*, WHO, accessed December 2021.