Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl (theophylline)

Evaluation statement

30 June 2022

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Subject of the evaluation

1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl (theophylline)

Chemicals in this evaluation

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1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compound with 2-aminoethanol (1:1)	573-41-1
1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, monohydrate	5967-84-0

Reason for the evaluation

An evaluation is needed to provide information on human health risks.

Parameters of evaluation

Theophylline and several derivatives are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation will examine whether these chemicals should be restricted to therapeutic use.

It should be noted theophylline is used as a therapeutic good (TGA 2022). As this is an excluded use under the *Industrial Chemicals Act 2019,* the risks from these uses have not been considered in this evaluation.

Summary of evaluation

Summary of introduction, use and end use

There is no specific information about the introduction, use and end use of these chemicals in Australia.

Based on international information, theophylline has reported industrial use in skin conditioning products (EC) and site limited use in chemical synthesis (ECHA BP). No industrial uses were identified for the other chemicals in this group.

Theophylline is listed in the Compilation of Ingredients Used in Cosmetics in the United States (Personal Care Products Council 2011), indicating use in 5 cosmetic products.

Theophylline has non-industrial uses in Australia as a therapeutic (TGA 2022).

Theophylline is listed in Schedules 3 and 4 of the *Poison Standard (TGA 2022)−The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)*. These entries preclude the supply of the chemical for use in industrial products (including cosmetic products).

Theophylline has been reported to be a High Production Volume chemical globally and is known to naturally occur in coffee and cocoa beans, and tea plants.

Theophylline is banned for use in cosmetic products in Canada and in Association of Southeast Asian Nations (ASEAN) countries.

Human health

Summary of health hazards

The critical health effect for risk characterisation is the long term systemic effect of developmental toxicity. These chemicals are also toxic if swallowed.

Based on the available data, theophylline is expected to cause specific adverse effects on development following oral exposure. The chemical may also be a testicular toxicant. Testicular effects were observed in some studies; however, effects were inconsistent between studies and occurred in conjunction with general toxicity. The ECHA Committee for Risk Assessment (RAC) concluded that there were no effects on sexual function or fertility that met the requirements for classification (ECHA 2020).

Developmental toxicity

The main effects considered to support the developmental toxicity classification are:

- A dose-dependent reduction of the number of live pups per litter in 5 consecutive litters, in a continuous breeding study in mice (ECHA 2020; Morrisey et al. 1988).
- A reduction of live pups per litter due to resorptions in a pre-natal developmental toxicity study in mice (ECHA 2020; NTP 1985).

In a pre-natal developmental toxicity study (conducted similarly to OECD TG 414), pregnant CD-1 mice (34–37/dose) were dosed with the chemical in drinking water at concentrations of 0, 750, 1500 or 2000 ppm (equivalent to 0, 282, 372 and 396 mg/kg bw/day) through gestation days 6 to 15. Pregnant mice were euthanised on gestational day 17. Clinical signs of toxicity included piloerection, rough coat and weight loss. At the 2 highest doses, maternal body weight gain during gestation (corrected for gravid uterine weight) was reduced and the percentage of resorptions per litter was increased. The reported NOAEL for maternal and developmental toxicity was 282 mg/kg bw/day (ECHA 2020; NPT 1985).

In a rat prenatal toxicity study (conducted similarly to OECD TG 414), pregnant (26–29/dose) Sprague Dawley rats were dosed with the chemical in feed at concentrations of 0, 1500, 3000 or 4000 (equivalent to ~0, 124, 218, and 259 mg/kg bw/day) through gestation days 6 to 15. Pregnant rats were euthanised on gestational day 20. Gestational weight gain was reduced at the highest dose (statistically significant) and at the mid dose (not statistically significant). Clinical signs of toxicity included piloerection and rough coat at the mid and high dose. The number of live foetuses per litter was decreased at the high dose group and the average male and female foetal weights per litter were decreased at mid and high dose. No statistically significant differences are reported for implantation sites, pre-implantation loss, and resorptions. No malformations or variations were reported (ECHA 2020; Lindstrom et al. 1990).

In a continuous breeding study, CD-1 mice (n=20/sex/dose; controls=40/sex) were dosed with theophylline via feed at 0, 750, 1500 or 3000 ppm (equivalent to 125, 265 or 530 mg/kg bw/day), daily, for 7 days prior to mating and during 14 weeks of cohabitation. The main parental toxicological effect was alopecia. The number of live pups per litter was reduced in all groups receiving theophylline. Mean live pup weight was decreased by 6% in the 530 mg/kg bw/day group. The number of days to deliver each litter was consistently increased in the 530 mg/kg bw/day dose groups. No maternal toxicity was observed except from the alopecia. Crossover mating indicated females were more susceptible as treated high dose females mated with control males also indicated a significantly reduced number of pups born alive and reduced live pup weights (ECHA 2020; Morrisey et al. 1988).

Sexual function and fertility

Testicular effects of reduced sperm density and seminal vesicle weight) were observed at the highest dose (530 mg/kg bw/day) in the continuous breeding study after 18 weeks (ECHA 2020; Morrisey et al. 1988). Decreased testes weight was also observed in a 14-week gavage study in mice at 300 mg/kg bw/day; however, it was associated with mortality at the same dose and reduced body weight in mid and high dose groups (NTP). Several other mouse studies showed no testicular effects at doses up to 800 mg/kg bw (ECHA 2020).

In a 19-week study in rats, significant increases in testicular histopathological effects (testes atrophy, oligospermatogenesis) was observed but only in conjunction with marked toxicity (increased mortality, reduced bw gain and food intake) (Weinberger et al. 1978). In 2 oral (diet/gavage) 14-week rat studies no biologically significant differences in sperm morphology were observed (ECHA 2020).

Information on effects in humans comes from studies where patients with asthma were given theophylline therapeutically. These studies do not indicate adverse effects that would warrant classification for adverse effects on development or fertility. Most studies evaluated for this chemical were reported to have negative effects on pregnancy outcome. The study designs (limited statistical power) did not make it possible to distinguish between the role of theophylline and the role of asthma itself in pregnancy outcomes. In 2 studies, an increase in preterm delivery was reported (ECHA 2020).

Hazard classifications relevant for worker health and safety

This group of chemicals satisfy the criteria for classification according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute Toxicity	Acute Tox. 3	H301: Toxic if swallowed
Reproductive and Developmental	Repr. 1B	H360D: May damage the unborn child.

Summary of health risk

Public

Current regulatory controls in Australia only allows the sale and supply of theophylline in pharmacy products or prescription medicines. The chemical is reported internationally to be present in cosmetic products, but the supply of theophylline for use in such products is not legal in Australia.

Based on the reported developmental effects it is not considered appropriate for this group of chemicals to be used in cosmetic products in Australia, and it is not proposed that any new entries be made in the Poisons Standard to allow for such use.

Workers

Current regulatory controls in Australia only allows the sale and supply of theophylline in pharmacy products or prescription medicines. Due to the lack of industrial use, the chemical does not pose a risk to workers in the industrial sector.

Conclusions

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

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.

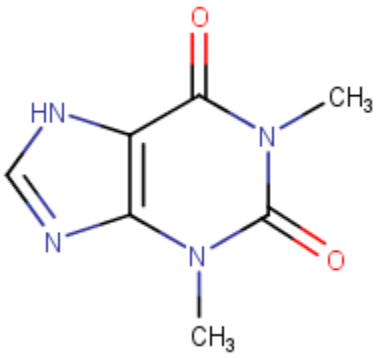
Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

Supporting information

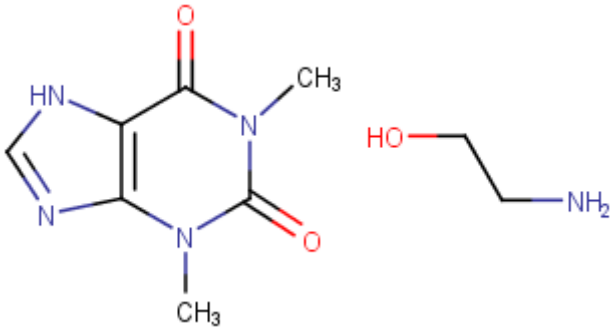
Grouping rationale

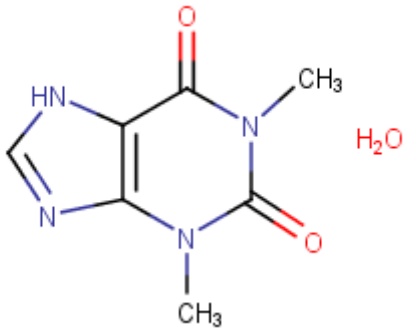
Chemicals in this group are 1H-purine-2,6-dione, 3,7-dihydro-1,3-dimethyl (theophylline), one salt and one hydrate. The listing of theophylline in Schedules 3 and 4 of the *Poison Standard* "includes preparations containing the chemical in any concentration and all salts and derivatives of the chemical unless it specifically states otherwise" (TGA 2022).

Chemical identity

Chemical name	1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-
CAS number	58-55-9
Synonyms	Theophylline; 1,3-dimethylxanthine; 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin; theocin.
Structural formula	
Molecular formula	$C_7H_8N_4O_2$
Molecular weight (g/mol)	180.166
SMILES	CN1C2=C(NC=N2)C(=O)N(C)C1=O
Chemical description	-

Chemical name	1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compound with 2-aminoethanol (1:1)
CAS number	573-41-1
Synonyms	Theophylline diethanolamide

Structural formula	
Molecular formula	$C_7H_8N_4O_2 .C_2H_7NO$
Molecular weight (g/mol)	241.25
SMILES	O=C1C=2NC=NC2N(C(=O)N1C)C.OCCN
Chemical description	-

Chemical name	1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, monohydrate
CAS number	5967-84-0
Synonyms	Theophylline monohydrate
Structural formula	
Molecular formula	$C_7H_8N_4O_2 .H_2O$
Molecular weight (g/mol)	198.18
SMILES	O=C1C=2NC=NC2N(C(=O)N1C)C.O
Chemical description	-

Relevant physical and chemical properties

The following information relates to theophylline (CAS No. 58-55-9)

Physical form	Solid white crystalline powder
Melting point	270–274 ˚C
Boiling point	454˚C (predicted)
Vapour pressure	683 x 10^{-9} Pa (predicted)
Water solubility	5.5 g L^{-1} at 19.9 ˚C
pKa	8.81
log K_{ow}	-0.0076 at 23 ˚C

Introduction and use

Australia

No specific industrial uses of these chemicals in Australia have been identified. These chemicals are not expected to be used industrially or in cosmetics in Australia due to its listing in Schedules 3 and 4 *of The Poison Standard* (TGA 2022) prohibiting industrial use.

Theophylline has non-industrial uses in Australia, including as a therapeutic. (TGA 2022).

International

The following international use information has been identified through the cosmetic ingredient database (EC), the European Chemicals Agency Brief Profile and Substance Information Card and Committee for Risk Assessment Reports and Dossiers (ECHA SI, ECHA BP, ECHA CLH), Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS 2001), SpecialChem Cosmetic Ingredients Selector (SpecialChem 2021), United States Food and Drug Administration (FDA 2000), and National Toxicology Program Toxicology and Carcinogenesis studies (NTP 1998).

Theophylline has reported cosmetic uses, including in skin conditioning cosmetic products.

Theophylline has reported site limited uses, including as an intermediate in the manufacture and synthesis of other substances.

Theophylline has reported non-industrial uses as a therapeutic, including as:

- a bronchodilator for the treatment of obstructive airway diseases such as bronchial asthma
- a myocardial stimulator
- anti-cellulite/thigh creams as a component of aminophylline at a concentration of less than 1% in cellulite reduction creams
- slimming and firming agents
- anti-inflammatories.

Theophylline naturally occurs in coffee and cocoa beans and in tea plants (*Thea sinensis)*. Theophylline is reported to be present in coffee beans and tea plants at concentrations of 5 and 200–400 mg/kg, respectively.

The chemical is listed on the OECD List of High Production Volume Chemicals (OECD 2004).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for this chemical.

Public

Theophylline is listed in the *Poisons Standard* (TGA 2022) as follows:

Schedule 3

Theophylline in liquid oral preparations containing 2 per cent or less of theophylline.

Schedule 4

Theophylline **except** when included in Schedule 3.

Schedule 3 chemicals are labelled with “Pharmacist Only Medicine”. The safe use of these chemicals require professional advice but should be available to the public from a pharmacist without a prescription.

Schedule 4 chemicals are labelled with “Prescription Only Medicine” or “Prescription Animal Remedy”. The use or supply of these chemicals should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.

Theophylline is not expected to be used industrially or in cosmetics in Australia due to its listing in Schedules 3 and 4 of The Poison Standard (TGA 2022) prohibiting industrial use.

Workers

Chemicals in this group are not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (Safe Work Australia).

International regulatory status

Canada

The use of theophylline in cosmetics is prohibited under Health Canada’s Cosmetic Ingredient Hotlist—List of Ingredients that are Prohibited for Use in Cosmetic Products (Government of Canada 2019).

Asia

The use of theophylline in cosmetics is restricted by the Association of Southeast Asian Nations (ASEAN) under the ASEAN Cosmetic Directive Annex II—list of substances which must not form part of the composition of cosmetic products (HSA 2019).

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