Anthranilic acid and its calcium salt: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Benzoic acid, 2-amino-	118-92-3
Benzoic acid, 2-amino-, calcium salt (2:1)	14342-65-5

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

Grouping Rationale

The chemicals in this group consist of the parent compound benzoic acid, 2-amino- (anthranilic acid; CAS No. 118-92-3) and its salt benzoic acid, 2-amino-, calcium salt (2:1) (calcium anthranilate; CAS No. 14342-65-5).

No exposure or hazard data are available for calcium anthranilate. In biological media, the counterion is not expected to drive toxicity (NICNAS) and this chemical is expected to have similar properties to the parent compound. Therefore, these chemicals are assessed together in this report.

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the United States (US) National Toxicology Program (NTP); and International Agency for Research on Cancer (IARC).

Anthranilic acid may be present in hair dyes as an impurity at up to 2 % (SCCNFP, 2003).

Anthranilic acid has reported site-limited use as an intermediate in the synthesis of dyes, perfumes and other chemicals.

Anthranilic acid has reported non-industrial use in:

- food preservatives;
- pesticides;
- veterinary medicine; and
- pharmaceuticals.

No industrial use information is available for calcium anthranilate; however, it is expected to have similar uses to anthranilic acid as an intermediate in the manufacture of dyes, perfumes and other chemicals.

Restrictions

Australian

Anthranilic acid is listed in the Australia Customs (Prohibited Imports) Regulations 1956 in Schedule 4 (Drugs).

The chemical is listed in the Code of Practice for Supply Diversion into Illicit Drug Manufacture—Category II: Illicit Drug Precursors/Reagents. An end-user declaration is required when the chemical is sold to non-account customers (Galleria Chemica).

International

Anthranilic acid is listed on the following (Galleria Chemica):

- Singapore Misuse of Drugs Act Third Schedule Controlled Equipment, Materials or Substances Useful for Manufacturing Controlled Drugs Part I & Part II;
- US Drug Enforcement Administration (DEA) List I and II Regulated Chemicals;
- United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances - Table II;
- Canada Controlled Drugs and Substances Act Schedule VI; and
- European Union (EU) Drug Precursors - Scheduled Substances Annex I Category 2.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

No hazard data are available for calcium anthranilate. Under biologically relevant conditions, calcium anthranilate is expected to dissociate to the calcium ion and the parent compound and; therefore, expected to have similar toxicological profile to anthranilic acid except for irritation and/or corrosion. Therefore, health hazard data for anthranilic acid are considered relevant for the assessment of both chemicals.

Toxicokinetics

Limited information is available.

Anthranilic acid is a tryptophan (plant derived amino acid) metabolite that occurs naturally in the body and is present in urine together with other tryptophan metabolites in humans (IARC, 1987).

The main metabolites of anthranilic acid in rats, rabbits and dogs are glucuronic acid and glycine conjugates. It has been suggested that anthranilic acid is hydroxylated at the 3- and 5-positions in rabbits and at the 3-position in rats. The hydroxylated derivatives of anthranilic acid, including 3-hydroxyanthranilic acid, have been reported for their toxicological properties as potential carcinogens (IARC, 1987).

Acute Toxicity

Oral

Based on the reported median lethal doses (LD50) in experimental animals, the chemicals are expected to have low acute oral toxicity.

The reported LD50 values for anthranilic acid from non-guideline studies are 4549 and 5410 mg/kg bw in rats and 1400 mg/kg bw in mice. Reported signs of toxicity included decreased locomotor activity, lack of coordination of muscle movements (ataxia) and deep breathing (Galleria Chemica; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

No reliable data are available.

In a non-guideline study, the application of anthranilic acid (50 % aqueous dispersion) on rabbit skin did not induce any skin irritation (REACH). No details of the test were available.

Eye Irritation

Based on the available data for anthranilic acid, the chemical causes serious eye damage and therefore warrants hazard classification. No data are available for calcium anthranilate. As the salt is expected to have a different irritant profile to the parent compound, the classification of anthranilic acid does not apply to calcium anthranilate.

In a non-guideline eye irritation study (10 days observation period with a scoring system similar to Draize), 2 Vienna White rabbits received a single application of solid anthranilic acid (~50 mm^3) in one eye while the other eye was treated with talcum powder as the control. The eyes were not rinsed after application. The average score for 2 animals over 24, 48 and 72 hours were 3 out of 3 for conjunctival redness and 3 out of 4 for corneal opacity (not reversible within 10 days). Iritis was observed in both animals (score 1 out of 2), but was fully reversible. Chemosis was only observed during the first 3 hours of the experiment. Scar formation at the upper eye lid was observed in 1 animal 10 days after the treatment (REACH). The chemical caused serious eye damage under the test conditions.

Sensitisation

Respiratory Sensitisation

Skin Sensitisation

Based on the limited data available, the chemicals are not expected to be skin sensitisers.

In a non-guideline local lymph node assay (LLNA) in mice, the reported stimulation indices (SI) were 0.09, 1.10 and 1.40 after treatment with concentrations of 10, 25 and 50 % of anthranilic acid in acetone/olive oil vehicle (4:1 v/v). The estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) was not calculated in the study because no SI value was ≥3. The chemical was considered a non-sensitiser (REACH). No further details of the test including the number of animals used were available.

The lack of skin sensitisation potential is supported by the lack of skin sensitisation alerts from quantitative structure-activity relationship (QSAR) predictions (QSAR Toolbox 4.2).

Repeated Dose Toxicity

Oral

Based on the limited data available, the chemicals are not considered to cause serious damage to human health from repeated oral exposure.

In a subchronic study conducted as part of a long-term carcinogenicity study, male Sprague Dawley (SD) rats and male Swiss mice (5/dose) received anthranilic acid in the diet at concentrations of 1000, 5000, 10000, 25000, or 50000 ppm (equivalent to ~90, 450, 900, 2250 or 4500 mg/kg bw/day for rats; and ~200, 1000, 2000, 5000 or 10000 mg/kg bw/day for mice), 7 days/week for 45 days followed by an additional 45 days of observation. Body weights were reduced by 11 and 17 % in rats receiving 25000 and 50000 ppm, respectively. No other adverse effects were reported. Body weights in mice were not affected. One mortality occurred among the mice, but was not considered treatment-related. Based on the available data, the no adverse effect levels (NOAELs) are 4500 and 10000 mg/kg bw/day for rats and mice, respectively (NTP TR-036, 1978).

Reduced body weights were observed in a 2-year carcinogenicity study, in rats at 15000 or 30000 ppm in the diet (equivalent to ~750 or 1500 mg/kg bw/day) and in mice at 25000 or 50000 ppm in diet (equivalent to ~3750 or 7500 mg/kg bw/day) (see

Carcinogenicity).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available data, the chemicals are not expected to be genotoxic. Anthranilic acid was negative in gene mutation studies in bacteria. The chemical showed both positive and negative results in in vitro mutation and clastogenicity studies in mammalian cells, but was negative for mutagenicity and clastogenicity in several in vivo studies.

In vitro

The following results were reported for anthranilic acid:

- negative in 2 bacterial reverse mutation assays (OECD TG 471) in *Salmonella typhimurium* strains TA98, 100, 1535 and 1537, with and without metabolic activation (S9) at concentrations of 100–6666 µg/plate (REACH; Zeiger et al, 1987);
- positive in 2 non-guideline mammalian somatic mutation tests in mouse or human lymphocytes, at concentrations of 250–1266 µg/mL in mouse lymphocytes and 1667 µg/mL in human lymphocytes (RTECS, 1988);
- positive in gene mutation studies at the thymidine kinase (tk) locus in L5178Y mouse lymphoma at concentrations above 1266 µg/mL without metabolic activation and at doses above 250 µg/mL with metabolic activation (NTP, 1988);
- negative in an unscheduled DNA synthesis assay (OECD TG 482) in rat hepatocytes without metabolic activation at concentrations of 0.73–1500 µg/mL (REACH);
- negative in a chromosome aberration (CA) assay in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations of 50–5000 µg/mL. One test gave a weakly positive result at 4000 µg/mL with metabolic activation, which was likely to be associated with moderate cytotoxicity (NTP, 1983);
- positive in a sister chromatid exchange (SCE) assay in CHO cells with and without metabolic activation at concentrations above 1500 µg/mL (NTP, 1983); and
- negative in a micronucleus (MN) assay in 3 p53-deficient rodent cell lines (V79, CHO and CHL) and in 3 p53-competent human cell lines (HuLy, TK6 and HepG2) with metabolic activation at concentrations up to 1371 µg/mL (Fowler et al., 2012).

In vivo

Negative results were reported for anthranilic acid in:

- a mammalian alkaline comet assay (OECD TG 489) and MN assays in SD rats orally exposed to the chemical at 500, 1000 or 2000 mg/kg bw at 3, 24 and 48 hours (Takasawa et al, 2015);
- a phosphatidylinositol glycan-class A (Pig-a) gene mutation and MN assays in male SD rats orally exposed to the chemical at 500, 1000 or 2000 mg/kg bw/day for 3 or 28 consecutive days (Dertinger et al, 2012);
- a mammalian MN assay (OECD TG 474) in ICR mice orally exposed to the chemical at 750, 1500 or 3000 mg/kg bw for males, and 600, 1200 or 2400 mg/kg bw for females (REACH); and
- mammalian SCE and CA assays in male B6C3F1 mice treated via the intraperitoneal (i.p.) route at doses of 100–500 mg/kg bw (NTP, 1985). Anthranilic acid was weakly positive at 600 mg/kg bw in this SCE assay; however, no statistical

data are available.

In silico (QSAR)

All the chemicals in this group and their microbial metabolites present alerts for mutagenicity based on their molecular structures as profiled by the OECD QSAR Toolbox v4.2. The presence of a primary aromatic amine presents an opportunity for interaction with deoxyribonucleic acid (DNA) molecules through nitrenium ion formation and through Michael (conjugate) addition for the hydroxylated metabolites. However, the mostly negative results from the available in vitro and in vivo studies indicate that the chemicals are not likely to be genotoxic.

Carcinogenicity

Based on the available data, the chemicals are not expected to be carcinogenic.

In a 2-year chronic study, Fischer 344 rats (35/sex/dose) and B6C3F1 mice (35/sex/dose) received anthranilic acid in diet at concentrations of 15000 or 30000 ppm (equivalent to ~750 or 1500 mg/kg bw/day) for rats, and 25000 or 50000 ppm for mice (equivalent to ~3750 or 7500 mg/kg bw/day) for 5 days/week for 78 weeks, and were observed for 26–27 weeks. There were no statistically significant increases in tumour incidence in any of the organs examined (including the urinary system) in either rats or mice (male or female) throughout the study (NTP TR-036, 1978).

In a non-guideline study, cholesterol pellets containing 20 % anthranilic acid were implanted into bladders of mice (n=75). Carcinomas of the bladder were observed in 10/75 mice within 12–15 months. In the control group (n=54) that received implants with cholesterol alone, 4/54 mice developed bladder carcinomas (IARC, 1976).

In another study, anthranilic acid was administered to CDF1 foetuses transplacentally for 13–17 days after conception (2040 mg/kg bw/day) or neonatally for 21 days (1345 mg/kg bw/day). The animals were observed for 1 year. No statistically significant tumorigenic outcome was observed in the study (RTECS, 1980).

Reproductive and Developmental Toxicity

Based on the limited information available, the chemicals are not expected to cause developmental toxicity. There are no data available for reproductive toxicity.

In a teratogenicity study, 10 female SD rats were administered 380 mg/kg bw of anthranilic acid by a single subcutaneous injection on day 9 or 16 of pregnancy. No teratogenic effects were observed (IARC, 1976). No further information is available.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation for anthranilic acid is serious eye damage.

Public Risk Characterisation

Given the international uses identified for the chemicals, it is unlikely that the public will be exposed to high concentrations of the chemicals.

The use of anthranilic acid and its salt in Australia is unknown. International data indicate that the chemical (anthranilic acid) is mainly used as an intermediate in chemical synthesis. The public could be exposed to the chemicals through potential impurities in hair dyes up to 2 % (see **Import, Manufacture and Use: International**). However, based on the low concentrations and that normal precautions are taken to avoid eye contact, anthranilic acid and its salt are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, dermal and ocular 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical local health effects, anthranilic acid may pose an unreasonable risk to workers unless adequate control measures to minimise ocular exposure to the chemical are implemented. The chemicals 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 HCIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals are considered to be sufficient, provided that the recommended amendment to the classification for anthranilic acid 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

Work Health and Safety

Anthranilic acid (CAS No. 118-92-3) is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards. This classification does not apply to calcium anthranilate (CAS 14342-65-5).

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318)

[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 industry

Control measures

Control measures to minimise the risk from ocular exposure to the chemicals 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 chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

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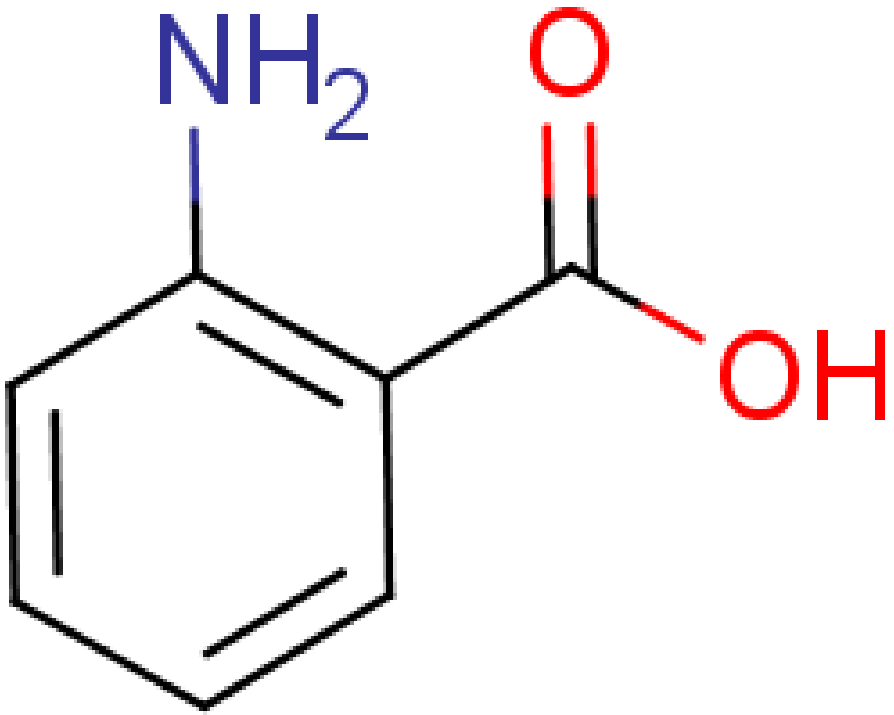
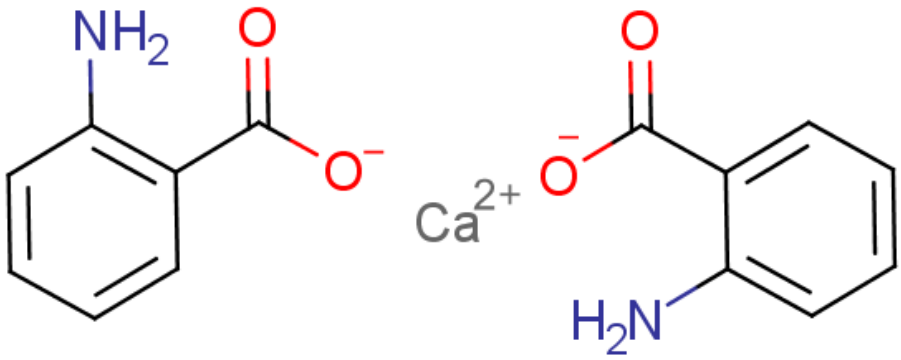
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Benzoic acid, 2-amino-** anthranilic acid o-aminobenzoic acid 1-amino-2-carboxybenzene 2-carboxyaniline
CAS Number	118-92-3
Structural Formula	

	
Molecular Formula	C7H7NO2
Molecular Weight	137.14

Chemical Name in the Inventory and Synonyms	**Benzoic acid, 2-amino-, calcium salt (2:1)** anthranilic acid, calcium salt (2:1) calcium anthranilate (1:2) calcium, 2-aminobenzoate
CAS Number	14342-65-5
Structural Formula	
Molecular Formula	C7H7NO2.1/2Ca
Molecular Weight	312.3

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