Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Benzenamine, N-phenyl-

Evaluation statement

14 December 2023

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Benzenamine, N-phenyl-

Chemical in this evaluation

Name	CAS registry number
Benzenamine, N-phenyl-	122-39-4

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation statement includes a human health risk assessment for all identified industrial uses of the chemical in Australia.

Summary of evaluation

Summary of introduction, use and end use

There is no specific information about the introduction, use or end use of the chemical in Australia.

Based on international information, the chemical is used in the manufacture of several chemical products. The chemical has identified uses in lubricants, and greases, hydraulic fluids, metal working fluids, in textile treatment products including leather and fur processing and dyes. The chemical is also a key ingredient in explosives. Consumer uses include motor and engine oils, transmission oil or high mileage oil filters. Concentrations up to 1.5% have been reported in consumer motor oils. The direct use as an additive in these consumer products is reported to be a minor use compared with the use of chemical products manufactured from this chemical.

The chemical is also used non-industrially as an anti-scalding agent in fruit storage solutions.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical. Based on the physicochemical properties, the chemical is expected to be readily absorbed following oral, dermal and inhalation exposure.

Based on the available data, the chemical is not irritating to skin and not a skin sensitiser.

The chemical has existing classifications for acute toxicity (oral, dermal and inhalation). While the available data do not support the current health hazard classifications, in the absence of more comprehensive information, there is insufficient evidence to warrant an amendment to the existing classifications.

Eye irritation effects have been reported in studies in animals; however, available data are insufficient to warrant classification for eye irritation.

The chemical has an existing classification for repeated dose toxicity. Based on the available data, the primary target organs for toxicity are the haematological system, the kidneys, spleen and liver. Effects have been observed in several species. The chemical is a methaemoglobin inducer, leading to regenerative anaemia (methaemoglobinaemia). In mice and rats, the chemical was reported to cause methaemoglobinaemia, anaemia, increased haematopoiesis of the bone marrow, splenic enlargement and hemosiderosis. Chronic nephropathy of the kidney was also observed.

Based on the limited data available, the chemical is not expected to cause specific adverse effects on fertility or development following oral exposure. Although some effects were observed on litter size and pup weights these were considered likely to be secondary to maternal toxicity.

There is sufficient evidence that the chemical has carcinogenic effects in animals. The chemical caused haemangioma, haemangiosarcoma, and haemangioma or haemangiosarcoma (combined) in various organs (liver, spleen, subcutis, bone marrow and heart) in rats and mice. The incidences of these tumour types were either significantly increased or exceeded the ranges of occurrences reported in historical controls. In female rats, adenocarcinoma of the uterus, and mononuclear cell leukaemia of the spleen was also reported. In addition, female mice were reported to have histiocytic sarcoma of the uterus. As there is no established mechanism to determine the carcinogenicity of the chemical, the relevance to humans cannot be ruled out. Although there is some evidence of genotoxicity in vitro, the chemical was negative in several in vivo studies.

No inhalation data are available.

For further details of the health hazard information see **Supporting Information**.

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity - oral	Acute Tox. 3	H301 Toxic if swallowed
Acute toxicity – dermal	Acute Tox. 3	H311 Toxic in contact with skin

Health hazards	Hazard category	Hazard statement
Acute toxicity – inhalation	Acute Tox. 3	H331 Toxic if inhaled
Specific target organ toxicity – repeat exposure	STOT RE 2	H373 May cause damage to organs through prolonged or repeated exposure
Carcinogenicity	Carc. 1B	H350 May cause cancer

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical at low concentrations (<1.5%) by incidental skin and eye contact with the chemical during use of domestic products. The frequency and duration of the use of such products is sufficiently low that exposure to the chemical would be considered intermittent. In addition, exposure to do it yourself (DIY) products is incidental, and normal precautions to avoid prolonged contact are expected. Although, the chemical is carcinogenic and causes systemic effects following repeated exposure there is uncertainty regarding the extrapolation from continuous exposure studies in animals to repeated, intermittent human exposures. The risk of chronic health effects to consumers at the high frequency of use cannot be ruled out; however, such risk is expected to be unlikely based on the low concentration of the chemical present in consumer products.

Margins of exposure (MOE) were calculated for occasional uses of DIY motor oils (Government of Canada 2020) using a NOAEL of 500 mg/kg body weight (bw)/day from a short term dermal study and adult systemic exposures up to 1.3 mg/kg bw/day. The MOE of 385 indicates that the chemical is unlikely to pose a risk of adverse systemic effects.

Based on the low use concentrations, the risk of eye irritation is considered to be low.

Overall, there are no identified risks to the public that require risk management for the chemical.

The chemical is currently listed on Appendix B (Substances considered not to require control by scheduling) of the Poisons Standard −Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) (TGA 2023), with the reason for inclusion being low toxicity. However, given the hazard profile of the chemical, an amendment to the entry may be appropriate.

Workers

During product formulation and packaging, dermal, oral, ocular 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 identified critical systemic effects and potential for carcinogenicity, the chemical could pose a risk to workers. Control measures to minimise dermal, oral, ocular and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Public

It is recommended that the delegate of the Secretary for Poisons Scheduling amend the entry in the *Poisons Standard* (SUSMP).

Consideration should be given to the following:

- the current entry in Appendix B is based on low toxicity
- the primary target organs for toxicity are the haematological system, kidneys, spleen and liver, for which these effects have been observed in several species
- there is sufficient evidence that the chemical has carcinogenic effects in animals.

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 oral, dermal, ocular and inhalation exposure to the chemical 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.
- 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 the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using this hazardous chemical depend on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health
- conducting air monitoring to ensure control measures in place are working effectively and continue to do so.

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

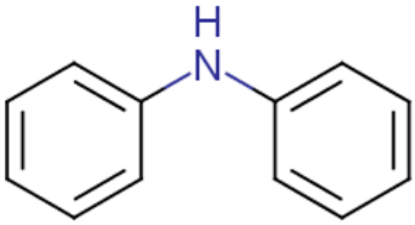
The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	benzenamine, N-phenyl
CAS No.	122-39-4
Synonyms	diphenylamine N-phenylbenzenamine N-phenylaniline
Molecular formula	C12H11N
Molecular weight (g/mol)	169.22
SMILES (canonical)	C=1C=CC(=CC1)NC=2C=CC=CC2
Chemical description	diphenylamine is composed of 2 phenyl rings joined by a secondary (2°) amine bond (CAS n.d.; NCBI n.d.)
Structural formula	

Relevant physical and chemical properties

The following physical and chemical properties were identified through various online services including: Scifinder, PubChem and Reach Dossiers (CAS n.d.; NCBI n.d.; REACH n.d.)

Physical form	Commonly a colourless, crystalline solid, but may be present with yellow hues.
Melting point	53–54 °C
Boiling point	302 °C
Vapour pressure	0.085 Pa (25 °C), 0.309 Pa (35 °C), 0.946 Pa (45 °C)

Water solubility	29.1mg/L (20 °C, pH 4), 24.4mg/L (20 °C, pH 7), 25.3mg/L (20 °C, pH 9),
Ionisable in the environment?	No
pKa	0.78±0.20 (20 °C) (Predicted)
log K_{ow}	3.82 (20 °C)

Introduction and use

Australia

No specific Australian introduction, use and end use information has been identified.

International

The following uses were identified from:

- the European Union Registration, Evaluation and Authorisation of Chemicals dossier (REACH)
- International assessment reports (EC 2008; EFSA 2012; Government of Canada 2020; IARC 2022; US EPA 2008)
- Galleria Chemica (Chemwatch n.d.)
- Substances in Preparations in Nordic Countries (SPIN) database.

Available information indicates that the chemical is widely used as an industrial chemical.

The major use identified for the chemical is site limited use including in the manufacture of chemical products including:

- antioxidants widely used in the rubber industry and for lubricants
- antiozonants used in the rubber industry
- stabilisers for plastics
- textile dyes.

The chemical has identified commercial use in:

- lubricants, greases and metal working fluids
- in textile treatment products including leather and fur processing
- as a stabiliser for nitro-based explosives and munitions
- adhesive and sealants.

Some of the commercial uses may also be used in domestic applications. Identified consumer uses include in motor/engine oil, transmission oil or high mileage oil filters. The direct use as an additive in these consumer products is reported to be a minor use compared with the use of chemicals manufactured from the chemical. Concentrations up to 1.5% have been reported in these consumer products (DeLima Associates n.d.; EC 2008; Government of Canada 2020).

There is some evidence of use as a stabiliser in perfume oils (EC 2008). However, this use was considered negligible in Europe in 2008 and based on international restrictions (see **International regulatory status**) is considered unlikely.

Non-industrial uses of the chemical include use in food processing as anti-scalding agents in fruit storage solutions.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

The chemical is listed in Appendix B in the Poisons Standard (SUSMP). Appendix B substances are considered not to require control by scheduling (TGA 2023).

Workers

The chemical is listed in the Hazardous Chemical Information System (HCIS) (Safe Work Australia, SWA) with the following hazard category and statements for human health:

Health hazards	Hazard category	Hazard statement
Acute toxicity - inhalation	Acute Tox. 3	H331 Toxic if inhaled
Acute toxicity - dermal	Acute Tox. 3	H311 Toxic in contact with skin
Acute toxicity - oral	Acute Tox. 3	H301 Toxic if swallowed
Specific target organ toxicity – repeat exposure	STOT RE 2	H373 May cause damage to organs through prolonged or repeated exposure

The chemical has an exposure standard of 10 mg/m^3 time weighted average (TWA) (SWA n.d.).

Safe Work Australia is currently reviewing workplace exposure standards (WES), including for diphenylamine. Further information about the review of WES is available on the SWA website (SWA 2023).

International regulatory status

Exposure standards

The following Protective Action Criteria (PAC) (formerly known as Temporary Emergency Exposure Limits (TEELs) are available for the chemical from the US Department of Energy (Chemwatch n.d.):

- PAC-1 = 30 mg/m^3

- PAC-2 = 180 mg/m^3
- PAC-3 = 220 mg/m^3

International regulations for the chemical time weighted exposure (TWA; 8-hour) are mostly consistent in the following countries having a TWA of 10 mg/m^3: Belgium, Canada, China, France, Ireland, New Zealand, Italy, Republic of Korea, Singapore, Spain, Switzerland, United Kingdom and United States of America (IFA n.d.).

Short term exposure limits (STEL; 15 minutes) of 10 mg/m^3 were reported for Austria, Denmark, Finland, Germany. In general, these countries have TWA lower than 10 mg/m^3. (IARC 2022; IFA n.d.).

Canada

The chemical is listed on the Cosmetic Ingredient Hotlist of ingredients that are Prohibited for use in cosmetic products (Chemwatch n.d.; Government of Canada 2022).

European Union

The chemical is listed in Annex II Cosmetic Products Regulation – List of substances prohibited in cosmetic products. The chemical is prohibited from use as a fragrance ingredient (Annex II/434) (Chemwatch n.d.).

New Zealand

The chemical is listed on the Cosmetic Products Group Standard as Schedule 4 – Components Cosmetic Products Must Not Contain (NZ EPA 2019).

United States of America

The chemical is listed on the Minnesota Department of Health, Chemicals of High Concern List 2022 (DeLima Associates n.d.).

The chemical is listed as a chemical of concern in California and New York due to its IARC classification (DeLima Associates n.d.).

Asia

The chemical is listed on the ASEAN Cosmetic Directive Annex II Part 1 – List of substances which must not form part of the composition of cosmetic products (Chemwatch n.d.; HSA 2023).

Other

The chemical is included in the Initial List of Perfumery Materials which must not Form Part of Fragrances Compounds Used in Cosmetic Products (SCCNFP 2000).

The International Fragrance Association (IFRA) prohibits the use of the chemical as a fragrance due to toxicity and teratogenicity concerns (IFRA n.d.).

Health hazard information

Toxicokinetics

In humans and in various experimental animals, the chemical was reported to be well absorbed in the gastrointestinal tract. In goats, the chemical was distributed as parent chemical (unchanged) or metabolites in the liver, kidney, leg muscle, loin muscle, back fat, omental fat and milk. In rats, tissue accumulation was not significant based on radiolabelled dose found in the carcass and tissues from a wide dose of 5 and 750 mg/kg bw.

The chemical is reported to be rapidly and extensively metabolised by hydroxylation followed by conjugation. In 2 human subjects, the chemical was metabolised to 4-hydroxy-diphenylamine and 4,4'-dihydroxydiphenylamine, following administration of a single oral dose of 100 mg of the chemical. The above metabolites together with unmetabolised chemical (parent compound) were found in the urine 24 hours after oral administration. Similar metabolites were reported in dogs. In rats, 12 different metabolites which include 4-hydroxy-diphenylamine, 4,4'-dihydroxydiphenylamine, sulfate and glucuronide conjugates of these metabolites were identified, where <3% of the administered dose remained as parent compound in the urine and faeces. In rabbits, 2-hydroxydiphenylamine was reported as a minor metabolite of the chemical (Alexander et al. 1965; FRMM 1978; IARC 2022).

In Sprague Dawley (SD) rats, up to 89% of 5 mg/kg bw [14C]-labelled chemical was recovered in the urine after 168 hours. In goats, up to 91% of the daily dose radiolabelled chemical (50 mg/kg bw/day; administered orally for 7 days) was recovered in the urine (IARC 2022). Urine is the major route of excretion of the chemical in rats, dogs, rabbits and goats, with bile excretion and faeces to a lesser extent.

When administered to Holstein cows the chemical was not detected in the milk or urine, but small traces were found in the faeces.

No data are available for dermal or inhalation absorption. Based on the molecular weight and log K_{ow} the chemical is expected to be bioavailable via these routes of exposure.

Acute toxicity

Oral

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Acute toxicity – Category 3; H301 (Toxic if swallowed)'. While the available data do not support the current health hazard classification, in the absence of more comprehensive information, there is insufficient evidence to warrant an amendment to the existing classification.

Two non-guideline studies were conducted and found an LD50 of 600 mg/kg bw in rats and gerbils, and >800 mg/kg bw in hamsters for oral acute toxicity (REACH 2008).

A non-guideline study on male Syrian hamsters, SD rats and Mongolian gerbils reported an LD50 of 600 mg/kg bw, >800 mg/kg bw and >800 mg/kg bw for each respective species. The study consisted of 10 animals/dose for the test group and 10 animals/dose in the control group. The chemical was administered in 3 doses (400, 600 or 800 mg/kg bw) by single daily gavage with exposure period of 3 consecutive days. A 100% mortality was reported in Syrian hamsters at 600 mg/kg bw and above. Brown kidneys and yellow brown papillomas were

reported at these doses. No mortality was reported in rats and gerbils (EC 2008; REACH N.D.).

In a study reported to be similar to current EU and OECD guidelines with 2 groups of 10 male rats each, an oral LD50 of > 5000 mg/kg bw was reported. Animals were administered doses of 3100 mg/kg bw or 5000 mg/kg bw in lutrol by gavage. After a 14 days observation period, no clinical signs and no mortality were observed in the 3100 mg/kg bw/day dosed group. Two animals died in the high dose group (EC 2008).

The Canadian Centre for Occupational Health and Safety Registry of Toxic Effects of Chemical Substances (RTECS) reports an LD50 average of 1142.5 mg/kg bw for rats and 1490mg/kg bw for mice. It is unclear whether these studies were GLP or OECD compliant. (CCOHS 2023)

Dermal

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as ‘Acute toxicity – Category 3; H311 (Toxic in contact with skin)’. While the available data do not support the current health hazard classification, in the absence of more comprehensive information, there is insufficient evidence to warrant an amendment to the existing classification.

Dermal LD50 values of >5000 mg/kg bw in rats and >2000 mg/kg bw in rabbits were reported. No other information was provided (EC 2008).

Inhalation

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as Acute toxicity – Category 3; H331 (Toxic if inhaled). No data are available to evaluate this endpoint.

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is not considered to be a skin irritant.

Two non-guideline skin irritation studies in Albino rats were reported. In the first study, the chemical was applied in the inner surface of the ears of 2 rabbits for 24 hours under occlusive application. No signs of irritation were reported during the 7 day observation period (EC 2008; REACH n.d.).

In the second study, the chemical (0.5 grams) was applied on 2 intact and 2 abraded skin sites in six rabbits for 24 hours under occlusive application. Very slight oedema was reported at the final reading of 72 hours (EC 2008; REACH n.d.).

Eye irritation

Data on eye irritating properties of the substance are conflicting and poorly documented. Although there are insufficient data to warrant classification of the chemical following ocular exposure, potential eye irritant effects of the chemical cannot be excluded.

In a study reportedly conducted according to EU and OECD Test Guidelines in 3 rabbits (strain not specified), the chemical (100 mg) was placed in the conjunctival sac of the left eye for each animal. The right eye served as a control. The study report indicated that eye irritation effects were not reversible after 21 days. No other information was provided (EC 2008; REACH n.d.).

In a study conducted similarly to OECD TG 405, instillation of the chemical (0.1 g) into the eye of 6 Albino rabbits, resulted in slight irritation within 24 hours but was fully reversed within 10 days. The chemical was reported to be slightly irritating (EC 2008; REACH n.d.).

In another study conducted according to OECD TG 405, the chemical (50 mg) caused moderate conjunctival irritation in 2 Albino rabbits. One of the animals had slight to moderate conjunctival irritation that persisted up to 7 days (EC 2008; REACH n.d.).

Sensitisation

Skin sensitisation

Based on the limited available data, the chemical is not expected to cause skin sensitisation.

A skin sensitisation study in guinea pigs reported that diphenylamine did not produce skin sensitisation reactions. No other information was provided.

In silico

No structural alerts for skin sensitisation were identified for the chemicals in this group using OECD QSAR Toolbox (OECD 2020), OASIS TIMES (optimized approach based on structural indices set–tissue metabolism simulator) (OASIS LMC n.d.), or the expert rule based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (Lhasa Limited n.d.). Application of skin metabolism and auto-oxidation simulators in QSAR Toolbox showed that the chemical produced no metabolites with skin sensitisation potential.

Observation in humans

Several studies in humans are available for the chemical and are reported below:

- No positive response was reported in a group of 11 male workers patch tested with 1% chemical in methanol (REACH n.d.).
- A woman 44 years of age with vesicular and exudative eczema on the back of her hand had a positive response when patch tested with the chemical. The woman handled metals, plastics and greases while working in a circuit bake factory (REACH n.d.). Positive patch test results were obtained in 3 out of 1012 eczema patients patch tested with 1% chemical in petrolatum. The positive result was reported as a cross reaction to p-phenylenediamine (REACH n.d.).
- No sensitisation reactions were reported in a maximisation test conducted in 30 volunteers tested with 1% chemical in petrolatum (REACH n.d.).

Repeat Dose Toxicity

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as Specific target organ toxicity – STOT RE 2; H373 (May cause damage to organs through prolonged or repeated exposure).

Based on the available data, the primary target organs for toxicity are the haematological system, kidneys, spleen and liver. Effects have been observed in several species. Effects in the blood and spleen including methaemoglobinaemia, anaemia, increased haematopoiesis of the bone marrow, splenic enlargement, haematopoiesis, and hemosiderosis. Chronic nephropathy of the kidney was also observed. Although results from individual studies may be insufficient to justify classification, the overall weight of evidence from all studies support the current classification.

Oral

In a 28 day study, Fischer rats received 111, 333 or 1000 mg/kg bw/day diphenylamine by gavage. Thirty six animals were divided into 6 groups (n=6, 4 groups being used for treatment and the remainder for investigation of recovery). Decrease in body weight gain, increase in liver, spleen and kidney weights, and anaemia were observed in the high dose group in both sexes. Histopathological findings included mucosal hyperplasia in the forestomach, dilatation, degeneration or necrosis of renal tubules in the corticomedullary junction and hyperplasia in the bone marrow. Slight increase in spleen, liver and kidney weights as well as slight degeneration of renal tubules were evident in several animals treated with 333 mg/kg bw/day. Recovery from histopathologic lesions and anaemia occurred after 14 days. A no observed adverse effect level (NOAEL) of 111 mg/kg bw/day were derived under these experimental conditions (EC 2008).

In a 90 day study, SD rats (10/dose) were administered the chemical in the diet at 0, 150, 1500, 7500 or 15000 ppm (approximately 0, 9.6, 96, 550 or 1200 mg/kg bw/day for males and 0, 12, 110, 650 or 1300 mg/kg bw/day for females). At doses ≥7500 ppm (≥550 mg/kg bw/day in males and ≥650 mg kg/bw/day), significantly decreased red blood cell counts and haemoglobin levels, indicating anaemia, were reported. In males, increases in absolute and relative liver and spleen weights, and in relative kidney and testes weights were observed. These were significant at the 2 highest doses. Incidence of haematopoiesis and pigment in the liver; haemosiderosis and congestion in the spleen; and pigmented kidneys in both sexes were also observed at the 2 highest doses. The spleens of all females at 1500 ppm also showed an increase from slight to minimal haematopoiesis and haemosiderosis. Dose related increases in absolute and relative liver weights were seen in females. The kidneys were dark in both sexes at 7500 and 15 000 ppm. A NOAEL of 150 ppm (9.6/12 mg/kg bw/day) was reported for this study (EC 2008; US EPA 2011; Government of Canada 2020).

In another non-guideline 90 day diet study, rats (unspecified strain, n=10/sex/dose) received a diet containing 0.01, 0.03, 0.1, 0.3 or 1 % of chemical (e 0, 9.8, 25, 78, 236, or 791 mg/kg-day for males and 0, 12, 32, 96, 303, or 978 mg/kg-day for females). Adverse effects in the blood, liver kidney and spleen were reported. Average haemoglobin values of female rats decreased slightly in a dose related manner. Organ weight changes were observed in all treated females and males receiving 0.1% (50 mg/kg bw/day) and higher doses. At 0.3% (150 mg/kg bw/day), liver, kidney and spleen appeared brown in colour and congestion occurred. At the 1.0% (500 mg/kg bw/day) dose, central lobular necrosis in the liver, increased nephritis in the kidneys, congestion in the spleen was observed. A lowest observed adverse effects level (LOAEL) of 0.03% (32 mg/kg/day) in female rats and 0.3% (236 mg/kg/day) in male rats was identified in this study because of a significant increase in relative liver weight (EC 2008; US EPA 2011).

In a 90 day study, both sexes of Swiss-derived CD-1 mice (15/dose) were administered the chemical in the diet at 0, 10, 525, 2625 or 5250 ppm (approximately 0, 1.7, 94, 444 or 926 mg/kg bw/day in males and 0, 2.1, 107, 555 or 1101 mg/kg bw/day for females). Dose related increases in the incidences and severity of lesions in the spleen and extra medullary

haematopoiesis in the liver were reported. At the 2 highest doses (2625 and 5250 ppm), statistically significant and dose related changes in red blood cell parameters and increases in liver and spleen weights were reported. At the highest dose, increased absolute kidney weights in males and increased relative kidney weights in females were observed. Statistically significant increase in incidences of splenic congestion and hemosiderosis and decreased in ovary weight was reported in females at 525 ppm. LOAEL values of 107 mg/kg/day in female mice and 444 mg/kg/day in male rats are identified in this study based on statistically significant increased incidences of congestion and hemosiderosis in the spleen. NOAELs of 2.1 mg/kg/day and 94 mg/kg/day are identified from this study in female and male rats, respectively (Government of Canada 2020, US EPA 2011). However, effects indicating significant haemolytic anaemia occurred at doses ≥2625 ppm (444/555 mg/kg bw/day).

Groups of 4 pure bred Beagle dogs of each sex received the chemical (purity, >99%) in gelatine capsules at doses of 0, 10, 25 or 50 mg/kg bw/day for 90 days. There were no deaths, and no treatment related changes were seen in body weights, food consumption, ophthalmological, haematological, clinical chemical, and urinary parameters. There were significant changes in organ weights, and gross and histopathological appearance.

Several longer term studies (1–2 years) are available in rats, mice and dogs (see **Carcinogenicity** section). Effects in the blood and spleen including methaemoglobinaemia, anaemia, increased haematopoiesis of the bone marrow, splenic enlargement, haematopoiesis, and hemosiderosis were observed. Chronic nephropathy of the kidney was also observed. NOAEL values in the range 7.5–73 mg/kg bw/day were reported. A comparison of the LOAEL values from longer term studies demonstrates that adverse effects in rats and dogs occurred at the same doses of about 25 mg/kg bw/day (EC 2008).

Dermal

In a dermal study, the chemical was applied on clipped skin of New Zealand White (NZW) rabbits (5/sex/dose) at 0, 100, 500 or 1000 mg/kg bw/day, 6 hours/day for 21 days under occlusive conditions. A dose dependent increase in the frequencies of dark red foci in the stomach at doses ≥500 mg/kg bw/day was reported in both sexes. A NOAEL of 100 mg/kg bw/day was determined (EC 2008; Government of Canada 2020).

In a 90 day dermal study, the chemical was applied onto the skin of SD rats at 0, 500 or 2000 mg/ kg bw/day for five days/week. All treated animals showed dermal hyperplasia at the application site. Increase in the relative kidney weights in the high dose males were reported. A NOAEL of 500 mg/kg bw/day was reported for systemic toxicity (EC 2008; Government of Canada 2020).

Inhalation

No data are available to evaluate this endpoint.

Genotoxicity

In vitro

In various bacterial reverse mutation studies including some conducted in accordance with OECD TG471, the chemical was not reported to be mutagenic in *Salmonella typhimurium* strains TA 1535, TA 1537, TA1538, TA 97, TA 98, TA102 and TA 100 strains at concentrations up to 500 µg/plate with and without metabolic activation. In a similar bacterial

mutation study, the chemical did not induce mutation in *S. typhimurium* strains TA1535, TA 1537, TA 98, TA 100, TA 1538 and *Escherichia coli* WP2 and WP uvrA with and without metabolic activation. Test concentrations were not provided (EC 2008; US EPA 2011; REACH n.d.).

In a bacterial reverse mutation study investigating potential mutagenicity of airborne particulate in rubber the manufacturing industry, Salmonella typhimurium, TA98NR, TA98, YG1021 and TA100 were treated with air particulate extracts collected over 2 hour periods, with and without metabolic activation. Positive results for direct and indirect frameshift mutagenicity in TA98NR, TA98 and YG1021 but not for TA100 were reported. Gas chromatography−mass spectrometry (GC-MS) analysis detected the presence of the chemical together with other chemicals from the air samples; however, it's concentration and effects on mutagenicity could not be quantified (IARC 2022; Fracasso et al. 1999).

In a mammalian chromosome aberration study conducted in accordance with OECD TG 473, the chemical was not clastogenic at concentrations up to 80 µg/mL without metabolic activation but was clastogenic at concentrations up to 65 µg/mL with metabolic activation in Chinese hamster ovary cells (REACH n.d.).

In a mammalian cell gene mutation study conducted in accordance with OECD TG 476, the chemical did not induce gene mutations at the thymidine kinase (TK) locus at concentrations up to 80 µg/mL without metabolic activation. However, weak positive results at concentrations up to 80 µg/mL with metabolic activation in mouse lymphoma L5178Y cells were reported. In a similar mammalian cell gene mutation study, the chemical did not induce gene mutations in mouse lymphoma L5178Y cells at concentrations up to 48.2 µg/mL in the presence of metabolic activation (EC 2008; REACH n.d.).

In an unscheduled DNA synthesis (UDS) in mammalian cells conducted in accordance with OECD TG 482, the chemical did not induce DNA damage in rat hepatocytes at concentrations up to 100 nmoles/mL (US EPA 2011, REACH n.d.). The chemical was also reported to be negative for DNA strand breaks in Chinese Hamster V79 lung cells, but no details of study were available (IARC 2022).

In a sister chromatid exchange (SCE) study conducted in accordance with OECD TG 479, increases in the frequency of SCE at concentrations up to 60 µg/mL in human adult non-smoking lymphocytes without metabolic activation was reported for the chemical. Short term exposure (4h) was negative with and without activation. However, continuous treatment without activation led to a 1.2-fold increase of the SCE frequency for the top dose (EC 2008; REACH n.d.).

A study that evaluated micronucleus formation in human peripheral lymphocytes (10,000/dose) treated with doses of 0.625, 1.25, 2.50, 5.0 or 10.0 µg/mL, reported a significant increase in micronucleus frequency at all concentrations including and higher than 1.25 µg/mL. The study suggested a potential cytogenetic effect of the chemical in human cells (IARC 2022).

In vivo

In an UDS in mammalian cells conducted in accordance with OECD TG486, male Fisher 344 rats (4 animals/sex/dose) were orally administered the chemical at 0, 750, 1500 or 2000 mg/kg bw. The chemical did not induce DNA damage in rat hepatocytes (REACH n.d.).

In a mammalian erythrocyte micronucleus study conducted in accordance with OECD TG474, 8-week-old ICR mouse (5 mice/sex/dose) were given single dose oral gavage of the

chemical at doses 250, 500 or 1000 mg/kg bw for males and 375, 750 or 1500 mg/kg bw for females. There was no increase in frequencies of micronucleated polychromatic erythrocytes in bone marrow cells indicating that the chemical is not clastogenic (chromosome damage) (EC 2008; REACH n.d.)

In a 90-day multiple endpoint study with dermal application of the chemical doses of 500 or 2000 mg/kg bw/day (see **repeated dose toxicity** section) no increases in micronucleated bone marrow erythrocytes were observed compared to untreated controls (EC 2008).

The chemical was negative in an intraperitoneal host mediated assay with mice as host and Salmonella typhimurium TA 1950 as indicator organism. Male NMRI mice were administered the chemical by gavage at concentrations of 1450–2900 µmol/kg bw
(US EPA 2011; IARC 2020).

A screening for induction of sister chromatid exchanges (SCE) in mice was negative. In this assay bone marrow cells were analysed after intraperitoneal administration of
1 to 100 mg/kg bw/day the chemical (EC 2008). No further details were available.

Reproductive and development toxicity

Based on the limited data available, the chemical is not expected to cause specific adverse effects on fertility or development following oral exposure. Although some effects were observed on litter size and pup weights these were considered likely to be secondary to maternal toxicity.

In a non-guideline 2 generation reproductive toxicity study (full study information not available), SD rats (28/sex/dose) received the chemical in feed daily at 0, 500, 1500 or 5000 ppm (equivalent to an average of 0, 40, 115, or 399 mg/kg bw/day for F0 males and 46, 131, or 448 mg/kg bw/day for F0 females during pre-mating). The total number of treatment days for parental males and females were not reported (EC 2008; US EPA 2011).

Systemic toxicity was observed at all doses in both sexes (dose-dependent). Adverse effects were more pronounced in females. Clinical signs of toxicity included: bluish coloured fluid in the cage and bluish coloured staining of the coat in both sexes and swelling of mammary gland(s) or palpable lateral-ventral masses (primarily in females) at 5000 ppm. Body weights were decreased at 5000 ppm in both sexes (6–9% in males, 5–8% in females) and at 1500 ppm in males (7–9% in males and 5–8% females) compared to controls. F1 animals were more severely affected than F0 animals. Bodyweights in F1 animals were decreased in both sexes at 5000 ppm (22–28% in males and 11–23% in females) and at 1500 ppm (7–9% in males and 5% in females). Food consumption (g/animal/day) was also decreased at 1500 and 5000 ppm. Organ weights including kidney, spleen and liver were different to controls at 5000 ppm in males and at 1500 and 5000 ppm in females (whether the weights were increased or decreased was not reported). The spleens were enlarged and had a blackish purple colour. Microscopic findings included brown pigment in the proximal convoluted tubules of the kidney, hepatocytic hypertrophy, brown pigments in liver Kupffer cells and congestion and hemosiderosis of the spleen. The reported NOAEL for the parental generations was 500 ppm (40 mg/kg bw/day in males and 46 mg/kg bw/day in females) based on the observed adverse effects in liver, kidney and spleen.

Smaller litter sizes at birth (significant for the F2 litters) were noted in both generations at 5000 ppm. No data on implantations were available. F1 pups had reduced bodyweights throughout lactation (11–25 %) at 5000 ppm. F2 had reduced bodyweights at 5000 ppm from lactation day (LD) 4 through 12, LD 21 (10%–29%) and at 1500 ppm on LD14 (10%) and LD21 (12%). The reported NOAEL for developmental toxicity was 500 ppm

(46 mg/kg bw/day) based on decreased F2 pup body weight in late lactation at 1500 ppm. The reported NOAEL for reproductive toxicity in maternal animals was 1500 ppm (131 mg/kg bw/day) based on decreased litter size in both generations.

In a 2 year chronic toxicity feeding study, a satellite group of Slonaker-Addis albino rats, 12 females and 3 males (5 weeks old) received the chemical in feed at 0.1, 0.25, or 0.50% (equivalent to approximately 50, 125, or 250 mg/kg bw/day) for 9 weeks before mating, 3 weeks during mating and until the end of the study. After all litters from the first mating had been weaned, rats were mated again. Offspring from the first mating was mated once to yield a second generation. Data for parental generations were not recorded
(EC 2008; USEPA 2011).

There were no effects on the numbers of litters born in the F0 generation (first and the second mating) or postnatal mortality in the F1 generation in any of the dose groups.

Litter sizes were reduced at the highest dose level (0.50%):

- F0 first mating, 6.3 pups/litter versus 8.3 pups/litter (control), $p<0.05$
- F0 second mating, 6.6 pups/litter versus 9.6 pups/litter (control), $p<0.01$
- F1 generation: 7.0 pups/litter versus 8.6 pups/litter (control).

No data on implantations were available. At the 0.50% dose level the offspring during lactation the offspring also gained less bodyweight during lactation compared to controls. Mean pup weights of the high dose group were lower than controls after the first mating, but not after the second mating. However, it was reduced in the second generation. While parental effects were not reported, data from the main study indicated that that the observed offspring body weight effects may be related to inadequate food intake of the dams during gestation and lactation. Reduced food intake and subsequently reduced body weight gain was reported from the main study for nonpregnant females at dietary levels of 0.50% and 1.0% of the chemical. The reported NOAEL for developmental toxicity was 0.25% (approximately 125 mg/kg bw/day).

In developmental studies in rats and rabbits, foetotoxic effects were not observed up to maternally toxic doses.

In a developmental toxicity study female SD rats (25/dose) were administered the chemical by gavage at 0,10, 50 or 100 mg/kg bw/day from gestational day (GD) 6 until GD 15. Dams had increased spleen weights, enlarged spleens and blackish, purple coloured spleens in the highest dose group. No developmental toxicity was observed at any dose level (EC 2008; Government of Canada 2020; REACH n.d.; USEPA 1998).

In a developmental toxicity study, female NZW rabbits (16–18/dose) were administered the chemical via oral intubation at 0, 33, 100 or 300 mg/kg bw/day on GD 7–19. At 300 mg/kg bw/day mean food consumption and bodyweight gain of dams were reduced. All treated animals had green discolouration of urine. There were no other clinical signs of toxicity or mortality during the study. Pregnancy rates were unaffected by the treatment. Litter size, litter weight, pre- and post implantation loss and mean foetal weight were not affected by the chemical in any of the dose groups. There were no malformations or anomalies that were considered treatment related (ECHA 2008; Government of Canada 2020; REACH n.d.).

Carcinogenicity

Based on the available data, there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In long term studies benign and malignant tumours were observed in multiple sites in 2 species and in both sexes, warranting hazard classification.

In a combined repeat dose and carcinogenicity study, compliant with GLP, Crj:BDF1 [B6D2F1/Crlj] mice (50/sex/dose) were fed daily with the chemical at doses of 0, 250, 1000, or 4000 ppm (w/w) for 104 weeks. At the highest dose, the survival rate was significantly lower in males and body weights were significantly decreased in both sexes. In males, a significant positive trend in the incidence of haemangioma in the liver, haemangioma or haemangiosarcoma (combined) in the liver and all organs (spleen, liver, subcutis, bone marrow and heart). At the intermediate dose (1000 ppm), the incidence of haemangioma or haemangiosarcoma (combined) was significantly increased in the spleen (9/50; 18%) and in all organs (14/50; 28%), which exceeded the range (0–14% spleen and 0–22%) reported in the historical controls. The incidences of haemangioma in all organs combined (10/50; 20%) was also significantly increased and exceeded the range (0–18%) reported in historical controls. In female mice, a significant increase of histiocytic sarcoma of the uterus was reported at the intermediate dose 17/50 (34%), which is at the upper bound of reported range (0–34%) in historical controls (IARC 2022; REACH n.d.).

A group of 125 male NMRI mice were gavaged with 300 mg/kg bw chemical in soybean oil, once a week for 18 months (approximately 78 weeks). A control group of 30 animals was used. Groups of animals were sacrificed at 26 weeks (28 treated animals), 52 weeks (24 treated animals) and the remaining animals were sacrificed at 126 weeks. There was no difference in the frequency of tumour types (most common tumour type: lymphoma and alveolar adenoma) reported between the treated and control animals (IARC 2022).

In a study according to OECD TG451, CD-1 mice (60/sex/dose) were fed daily with the chemical (in corn oil) in plain diet at doses of 0, 525, 2625 or 5250 ppm (approximately 0, 73, 370 or 760 mg/kg bw/day for males and 0, 91, 460 or 940 mg/kg bw/day for females) for 18 months. The study reported treatment related mortality and significant reduction in body weight. The incidence of tumours was comparable in the treated and control groups (US EPA 2011; REACH n.d.).

In a 92-week study in CD-1 mice (150/sex/dose) no effects were noted including the timing or incidence of tumours following exposure in the diet at doses up to 45 mg/kg bw/day) (US EPA 2011).

In combined repeat dose and carcinogenicity study, compliant with GLP, F344/DuCrlCrlj rats (50/sex/dose) were fed daily with the chemical at doses of 0, 250, 1000 or 4000 ppm (w/w) for 104 weeks. No difference in survival rates between the treated and the control groups in both sexes were reported. Body weights in both sexes in the highest group, and body weights in females in the intermediate group were significantly lower compared to the control group. Similarly, food consumption in both sexes in the highest group and food consumption in females in the intermediate group were significantly reduced compared to the control group. In male rats, a significant positive trend in the incidence of haemangiosarcoma in the spleen (6%), and in all organs (spleen and subcutis) combined (8%); and haemangioma or haemangiosarcoma (combined) in the spleen (6%) and in all organs combined (10%) were reported. All exceeded the range (0–4%) in the historical control. The incidence of haemangioma or haemangiosarcoma (combined) in all organs was significantly increased at the highest dose. A significant increase in fibroma (11/50) and fibroma or fibrosarcoma (combined) (13/50) in the subcutis was reported in the lowest group. A significant positive

trend in the incidence of interstitial cell tumour of the testes was also reported, with significant increases at the intermediate and high dose groups. In female rats, a significant positive trend in the incidence of adenocarcinoma, and adenoma and adenocarcinoma (combined) of the uterus, and mononuclear cell leukaemia of the spleen was reported. The significant increase in incidence of adenocarcinoma (8%), and adenoma and adenocarcinoma (combined) (8%) of the uterus at the highest dose exceeded the range (0-4%) in the historical control (IARC 2022; REACH n.d.).

A study following OECD TG 453 and EPA OPP 83-5, Sprague Dawley rats (60/sex/dose) were fed with the chemical in plain diet at doses of 0, 200, 750, 3750 or 7500 ppm (approximately 8.1, 29, 150 or 300 mg/kg bw/day) (males) or 0, 150, 500, 2500 or 5000 ppm (approximately 7.5, 25, 140 or 290 mg/kg bw/day) (females) for 12 or 24 months. There was no mortality for the duration of the study. No treatment related increase in tumour incidence was observed. (EC 2008; REACH n.d.).

A group of weanling Slonaker-Addis strain rats (20/sex/dose) were fed with the chemical at concentrations of 0, 1.001%, 0.01%, 0.1%, 0.5%, or 1.0% for 2 years. No increase in the frequency of any tumour types was reported (IARC 2022).

Female SD rats (20) were given a single dose of 300 mg/rat of the chemical in sesame oil by gavage and sacrificed 6 months after treatment. Two animals died during the study. No increased in the incidence of tumours of any type was reported (IARC 2022; REACH n.d.).

Beagle dogs (2/sex/dose) were fed with the chemical at concentration of 0, 0.01%, 0.1% or 1.0% (equivalent to 0, 2.5, 25, or 250 mg/kg bw/day) for 2 years. No incidence of tumours was reported in all treatment groups (US EPA 2011, Government of Canada 2020, IARC 2022). However, high incidence of spontaneous haemangiosarcoma have been reported to occur in numerous breeds of dogs (Cohen et al. 2009).

The International Agency for Research on Cancer (IARC) has classified the chemical as Group 2B Carcinogen – Possibly carcinogenic to humans, based on sufficient evidence for cancer in experimental animals. There is some evidence that the chemical has key characteristics of carcinogens (IARC 2022).

References

AICIS (Australian Industrial Chemicals Introduction Scheme) (2021) Chemicals that are unlikely to require further regulation to manage risks to health, AICIS, accessed 25 September 2023.

Alexander WE, Ryan AJ, Wright SE. (1965) Metabolism of diphenylamine in the rat, rabbit and man, *Food and Cosmetics Toxicology*, Volume 3, pages 571-579, doi.org/10.1016/S0015-6264(65)80203-6

CAS (Chemical Abstracts Service) (n.d.) CAS SciFinder[n], CAS website, accessed 25 September 2023.

CCOHS (Canadian Centre for Occupational Health and Safety) (2023) *Record for Chemical name Diphenylamine, CAS No 122-39-4*, CCOHS, accessed 25 September 2023.

Chemwatch (n.d.) *Galleria Chemica*, Chemwatch website, accessed 25 September 2023.

Cohen SM, Storer RD, Criswell KA, Doerrer NG, Dellarco VL, Pegg DG, Wojcinski ZW, Malarkey DE, Jacobs AC, Klaunig JE, Swenberg JA and Cook JC (2009) 'Hemangiosarcoma in rodents: mode-of-action evaluation and human relevance', *Toxicological Sciences*, Volume 111, Issue 1, September 2009, Pages 4–18

DeLima Associates (n.d.) *Consumer Product Information Database*, DeLima Associates website, accessed 25 September 2023.

ECHA (European Chemicals Agency) (2008) *Diphenylamine – Summary Risk Assessment Report,* ECHA, accessed 25 September 2023.

EFSA (European Food Safety Authority) (2012) *Conclusion on the peer review of the pesticide risk assessment of the active substance diphenylamine*, EFSA, accessed 25 September 2023.

Fracasso ME, Franceschetti P, Mossini E, Tieghi S, Perbellini L and Romeo L (1999) 'Exposure to mutagenic airborne particulate in a rubber manufacturing plant', *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, Volume 441, Pages 43-51, doi.org/10.1016/S1383-5718(99)00033-9

Fragrance Raw Materials Monographs (FRMM) (1978) Diphenylamine, Food and Cosmetics Toxicology, Volume 16, pages 723-727, doi.org/10.1016/S0015-6264(78)80090-X

Government of Canada (2020) *Draft screening assessment – Aromatic Amines Group*, Government of Canada, accessed 25 September 2023

Government of Canada (2022) *Cosmetic Ingredient Hotlist - List of Ingredients that are Prohibited for Use in Cosmetic Products*, Government of Canada, accessed 25 September 2023.

HSA (Health Sciences Authority) (2023) *Annexes of the ASEAN Cosmetic Directive – Annex II– Part 1: List of substances which must not form part of the composition of cosmetic products*, HSA, accessed 25 September 2023.

IARC (International Agency for Research on Cancer) (2022) *1,1,1-Trichloroethane and Four Other Industrial Chemicals IARC Monographs on the Identification of Carcinogenic Hazards to Humans Volume 130*, IARC, accessed 25 September 2023.

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (n. d.) *GESTIS international Limit Values – Diphenylamine*, IFA website, accessed 25 September 2023.

IFRA (International Fragrance Association) (n.d.) Diphenylamine amendment 38 document, IFRA website, accessed 25 September 2023

Lhasa Limited, Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (Version 6.0.1), [Computer software], Lhasa Limited website, accessed 25 September 2023.

NCBI (National Centre for Biotechnology Information) (n.d.) *PubChem*, NCBI website, accessed 25 September 2023.

NZ EPA (New Zealand Environmental protection Agency (2019) *Cosmetic Products Group Standard Additional Schedules*, Schedule 4, NZ EPA accessed 25 September 2023

OASIS LMC (Laboratory of Mathematical Chemistry) Optimised Approach based on Structural Indices Set–TIssue MEtabolism Simulator (OASIS–TIMES) (Version 2.28.1.6), [Computer software], LMC, accessed 21 June 2023.

OECD (Organisation for Economic Co-operation and Development) (2020) Quantitative Structure-Activity Relationship (QSAR) Toolbox (Version 4.4.1) [Computer software], OECD website, accessed 9 August 2023.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.) *Registration dossier for diphenylamine, CAS No. 122-39-4*, European Chemicals Agency website, accessed 25 September 2023.

SCCNFP (Scientific Committee on Cosmetic Products and Non-Food products) (2000) *An Initial List of Perfumery Materials Which Must Not Form Part of Fragrances Compounds Used in Cosmetic Products*, SCCNFP, accessed 25 September 2023.

SPIN (Substances in Preparation in Nordic Countries) (n.d.) *SPIN Database*, SPIN website, accessed 25 September 2023.

SWA (2023) Workplace Exposure Standards Review, SWA website, accessed 25 September 2023.

SWA (n.d.) Hazardous Chemical Information System, SWA website, accessed 25 September 2023.

TGA (Therapeutic Goods Administration) (2023) *Standard for the Uniform Scheduling of Medicines and Poisons No.41 (Poisons Standard July 2023)*, TGA, accessed 25 September 2023.

UNECE (United Nations Economic Commission for Europe) (2017) *Globally Harmonized System of Classification and Labelling of Chemicals (GHS) 7th Revised Edition*, UNECE, accessed 25 September 2023.

USEPA (United States Environmental Protection Agency) (1998) *Reregistration Eligibility Decision – Diphenylamine; CASRN 122-39-4*, USEPA, accessed 25 September 2023.

USEPA (United States Environmental Protection Agency) (2011) *Provisional Peer-Reviewed Toxicity Values for Diphenylamine (CASRN 122-39-4)* USEPA, accessed 25 September 2023