Australian Government
Department of Health, Disability and Ageing
Australian Industrial Chemicals Introduction Scheme

2-Pyrrolidinone

Evaluation statement (EVA00193)

1 April 2026

Draft

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AICIS evaluation statement

Subject of the evaluation

2-Pyrrolidinone

Chemical in this evaluation

CAS name	CAS number
2-Pyrrolidinone	616-45-5

Reason for the evaluation

New information is available about human health risks.

Parameters of evaluation

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

The chemical was previously assessed under the National Industrial Chemicals Introduction and Assessment Scheme (NICNAS 2013a). The chemical was published as a Tier I assessment. Based on available data the chemical was considered not to pose an unreasonable risk to workers and public health at the time of the NICNAS publication. New information has become available regarding developmental toxicity and potential for public exposure.

Therefore, this evaluation will:

- provide information on all identified hazards and risks
- review the weight of evidence, including new toxicity and use information
- consider whether any means for managing risks are required based on the new information.

Summary of evaluation

Summary of introduction, use and end use

There is currently limited specific information about the introduction, use and end use of the chemical in Australia. Publicly available information indicates use in inks for ink jet printing sold in Australia at concentrations up to 20%.

Based on the international use information, the chemical has reported site-limited and commercial uses in:

- ink, toner and colourant products
- paint and coating products
- adhesive products
- manufacture of paper products
- fabric, textile and leather products
- manufacture of chemicals including polymers and plastics.

Use in inks and toners in printer cartridges supplied to the public have been reported with concentrations in the range of 1–<30%, internationally. Based on the available data, the chemical is not likely to be used in personal care products (cosmetics).

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical. Data for 2 structurally similar chemicals, N-methyl pyrrolidone (CAS No. 872-50-4) and N-ethyl pyrrolidone (CAS No. 2687-91-4) have been used to support conclusions on health hazards where required.

The chemical has been shown to be absorbed following oral and dermal exposure.

Based on the available data, the chemical:

- has low acute oral, dermal and inhalation toxicity
- is not a skin irritant
- is not a skin sensitiser
- is not expected to cause serious systemic health effects following repeated oral exposure
- is not likely to be genotoxic
- is not likely to be carcinogenic
- is not likely to cause to cause adverse effects on fertility or sexual function.

The chemical is reported to cause mild eye irritation in a rabbit eye irritation study. Corneal opacity was observed in both animals. These effects were fully reversible in 7 days.

Based on the available data, there is clear evidence of specific adverse effects on foetal development in animals at high doses. The chemical caused high concern malformations in rats and rabbits, with effects in rabbits occurring at the highest dose tested of 1000 mg/kg bw/day. This included effects on the cardiovascular system. The NOAEL for prenatal developmental toxicity in rabbits was determined to be 250 mg/kg bw/day based on the increased foetal malformations and increased late resorptions in the 1000 mg/kg bw/day dose group, and reduced foetal body weight in the 500 and 1000 mg/kg bw/day dose groups. The NOAEL for prenatal developmental toxicity in rats was determined to be 600 mg/kg bw/day based on the reduced foetal body weight and increased visceral and skeletal malformations observed in the 1900 mg/kg bw/day dose group (highest dose tested). Maternal toxicity was observed in some animals at the doses associated with malformations. However, malformations also occurred in offspring of animals without signs of maternal toxicity, indicating a direct effect of the chemical on development. Observed effects are

similar to those observed for N-methyl pyrrolidone and N-ethyl pyrrolidone which are classified for developmental toxicity.

Limited repeat dose 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 does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Serious eye damage/eye irritation	Eye Irrit. 2B	H320: Causes eye irritation
Reproductive toxicity	Repr. 1B	H360D: May damage the unborn child

Summary of health risk

Public

Based on the available use information, public exposure will be limited to use of the chemical in inkjet cartridges. Due to the design of the cartridges, exposure to the chemical should be low and incidental in nature (accidental dermal contact and inhalation while ink is drying). Once inks and coatings are cured, the chemical is not expected to be available for exposure. Developmental effects have only been observed in animals at high doses. Therefore, there are no identified risks to the public that require management. However, if information becomes available indicating the chemical has other consumer uses, further risk management may be required.

Workers

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

Proposed means for managing risk

Inventory listing

To manage the potential risks to public health from the introduction and use of the chemical, the Inventory listing should be varied to add a new term of listing under *section 86* of the *Industrial Chemicals (IC) Act 2019*.

Term of listing	Details
Specific requirements to provide information to the Executive Director under *section 101* of the *IC Act*	A person who introduces this chemical must tell the Executive Director the volume of introduction and end use of the chemical within 20 working days if the chemical is being introduced for consumer end use, except end use in toner/printer cartridges.

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 (see **Summary of health hazards** section).

A Specific Concentration Limit (SCL) of 3% is recommended as the cut-off concentration for classification (see **Supporting information**).

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.

Recommended control measures that could be implemented to manage the risk arising from dermal, ocular and inhalation exposure to this chemical includes, but is not limited to:

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

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.

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

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 proposes to be satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

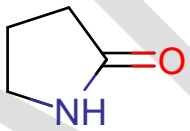
The risk conclusions for the public are driven by the evaluation finding that consumer use of the chemical is expected to be limited to use in toner/printer cartridges. Limited public exposure and risk is expected from this end use. Given its potential to cause adverse effects on foetal development, identification of an introduction for any new consumer end use of the chemical in Australia is considered necessary to ensure appropriate risk management. Therefore, a variation to the listing for the chemical – to add a specific information requirement – is proposed to manage the risks to human health from the introduction or use of the industrial chemical (see **Proposed means of managing risk**).

Note:

1. Obligations to report additional information about hazards under *section 100* of the *Industrial Chemicals Act 2019* apply.
2. A person introducing this chemical should be aware of their obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	616-45-5
CAS name	2-Pyrrolidinone
Molecular formula	C_4H_7NO
Associated names	2-Pyrrolidone
Molecular weight (g/mol)	85.10
SMILES (canonical)	O=C1NCCC1
Structural formula	

Relevant physical and chemical properties

Physical form	Liquid
Melting point	25°C
Boiling point	251°C
Vapour pressure	1.75 Pa at 24.6°C
Water solubility	679.7 g/L at 20°C
pK_a	14.7
log K_{ow}	0.71 at 25°C

Introduction and use

Australia

There is currently limited specific information about the introduction, use and end use of the chemical in Australia. An online search of safety data sheets identified that the chemical is used in inks for ink jet printing at concentrations up to 20% in Australia.

International

The following international uses have been identified by:

- ECHA Chemicals Database (ECHA n.d.)
- Registration, Evaluation, Authorisation and Restriction of Chemicals dossier (REACH n.d.)
- European Chemicals Agency documents (ECHA 2023; ECHA 2024)
- Substances and Preparations in the Nordic countries (SPIN n.d.)
- United States Environmental Protection Agency (US EPA) Chemical Data Reporting (US EPA 2020)
- US EPA CompTox Chemicals Dashboard (US EPA n.d.)
- Government of Canada inventory update reporting (Government of Canada 2017).

The chemical has reported site-limited uses with functional use as an intermediate and solvent, including in the manufacture of:

- chemicals, as well as plastic and polymer products
- paper products.

The chemical has reported commercial uses, including in:

- inks and toners, as well as printer cartridges
- paints and coatings, as well as paint strippers/removers
- adhesives
- textiles and apparel.

Use in inks and toners in printer cartridges supplied to the public have been reported with concentrations in the range of 1–<30%, internationally (Government of Canada 2017; US EPA 2020). No consumer uses were reported under REACH.

The chemical is listed in the International Nomenclature of Cosmetic Ingredients (INCI) database *'as a reference for the definition of other INCI Names and might not be a marketed cosmetic ingredient.'* (Personal Care Products Council n.d.). Online product searches do not indicate that the chemical is present in cosmetic products (EWG n.d.; INCI beauty n.d.). The chemical is not listed on the IFRA transparency list (IFRA n.d.)

The chemical has reported non-industrial use as a flavour.

Existing Australian regulatory controls

Public

No specific controls are currently available for the industrial use of this chemical.

Workers

The chemical is not listed on the Hazardous Chemical Information System, and no specific exposure standard is available in Australia (SWA n.d.).

International regulatory status

Exposure standards

The following exposure standards were identified for the chemical: time weighted average (TWA) and short term exposure limit (STEL) of 10 mg/m^3 in Russia and Belarus respectively (Chemwatch n.d.).

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 = 52 mg/m^3
- PAC-2 = 590 mg/m^3
- PAC-3 = 3400 mg/m^3

Health hazard information

The chemical 2-pyrrolidinone (CAS No. 616-45-5) is structurally similar to chemicals N-methyl-2-pyrrolidone (NMP, CAS No. 872-50-4) and N-ethyl-2-pyrrolidone (CAS No. 2687-91-4). Data on these chemicals have been used as read across to support conclusions on health hazards where required.

Toxicokinetics

A toxicokinetic study conducted in Sprague Dawley (SD) rats using a radiolabelled mixture of 2-pyrrolidinone and N-methyl-2-pyrrolidinone (NMP) administered by either oral gavage or dermal application showed that systemic absorption occurred more rapidly following oral exposure. Peak plasma radioactivity was observed approximately 2 hours after oral dosing in both sexes. In contrast, dermal absorption progressed more slowly, with relatively stable plasma concentrations over the first 6 hours and maximal levels occurring at 6 hours in males and 2 hours in females. The terminal elimination half-life of total plasma radioactivity following oral exposure was 29 hours in males and 27 hours in females (Midgley et al. 1992; REACH n.d.).

In both oral and dermal studies, the parent compounds (2-pyrrolidinone and NMP in the test mixture) accounted for approximately 80% of circulating radioactivity up to 8 hours post-exposure. This indicated limited first-pass metabolism during the early phase of distribution. Beyond this time, biotransformation became more evident, and by 12 hours most of the plasma radioactivity consisted of unidentified polar metabolites. Excretion occurred primarily via the urine, which accounted for 85–88% of the administered oral dose and 61–70% of the dermal dose within 24 hours. Minor proportions of radioactivity were eliminated in faeces (1–2%) and expired air as CO_2 (6–7%) regardless of the exposure route.

The metabolism of 2-pyrrolidinone is similar to that of N-methyl pyrrolidone (CAS No. 872-50-4) (NICNAS 2013b). Additional metabolic investigations in swine (pigs) demonstrated that 2-pyrrolidinone undergoes sequential oxidation, initially forming 5-hydroxy-2-pyrrolidinone and subsequently, succinimide, with metabolite levels increasing over the first 12 hours after intramuscular administration. In cattle, succinimide formation was comparatively limited even after 12 hours. Across these species, the parent chemical together with 5-hydroxy-2-pyrrolidinone and succinimide accounted for roughly 80% of

urinary radioactivity. A portion of the radiolabel was also incorporated into endogenous metabolites, including amino acids, fatty acids, urea, and expired CO_2 (EMA 1998).

In mammals, 2-pyrrolidinone is linked to the metabolic pathways of glutamic acid, putrescine, and gamma aminobutyric acid (GABA). Evidence suggests that 2-pyrrolidinone, as a cyclic analogue of GABA, can act as a biochemical precursor of GABA within the central nervous system. The compound is capable of crossing the blood–brain barrier and can undergo enzymatic hydrolysis to form GABA *in vivo*. However, this conversion appears to be tightly controlled by homeostatic mechanisms, preventing excessive or unregulated GABA production (EMA 1998).

Acute toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity.

In a GLP compliant acute oral toxicity study conducted in accordance with OECD TG 401, SD rats (5/sex/dose) were treated with a single dose of the chemical (2000 mg/kg bw) by gavage. The median lethal dose (LD50) was reported to be >2000 mg/kg bw. A reported sublethal sign of toxicity included hunched posture (REACH n.d.).

In other studies, for which limited details were available, the LD50 was reported to be 5000–9486 mg/kg bw in rats, 7280 mg/kg bw in guinea pigs, and 9000 mg/kg bw in mice (REACH n.d.). Reported sublethal signs of toxicity in rats included:

- convulsions
- paralysis
- apathy
- lateral or prone position
- staggering
- salivation
- intermittent breathing.

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD TG 402, the chemical (2000 mg/kg bw) was applied topically for 24 hours in an occlusive manner to New Zealand White (NZW) rabbits (5/sex/dose). The LD50 was reported to be >2000 mg/kg bw (REACH n.d.).

Inhalation

Based on the available data, the chemical is likely to have low acute inhalation toxicity

There were no mortality or signs of overt toxicity in animals exposed to the saturated vapour pressure. In a non-GLP compliant acute inhalation toxicity study conducted in accordance with OECD TG 403, Hannover rats (6/sex/dose) were exposed to the chemical as a vapour (inhalation exposure type unspecified) for 8 hours at a concentration of 0.061 mg/L (saturated test atmosphere). No mortality was reported (REACH n.d.).

The structurally related chemical NMP has low acute inhalation toxicity with a median lethal concentration (LC50) >5.1 mg/L (NICNAS 2013b).

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is at most a slight skin irritant particularly with prolonged skin contact.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 NZW rabbits (sex unspecified) were treated with the chemical for 4 hours in a semi-occlusive manner. Observations were recorded at 1, 24, 48 and 72 hours after patch removal. Mean scores for individual animals (based on 24, 48 and 72 hour observations) were zero for both erythema and oedema. Very slight erythema was reported at the 1 hr observation period but was reversible within 24 hours (REACH n.d.).

In a non-guideline skin irritation study, 6 male Vienna white rabbits were treated with the chemical for 24 hours in an occlusive manner and observed for 8 days. The following mean erythema scores (based on 24, 48 and 72-hour observations) for individual animals were reported: 1, 1, 0.7, 1, 1.7, and 1. The mean oedema score (based on 24, 48 and 72 hour observations) was 0 for all animals (REACH n.d.).

In a non-guideline skin irritation study, 2 Vienna white rabbits (sex unspecified) were treated with the chemical for 20 hours in an occlusive manner and observed for 8 days. The following mean erythema scores (based on 24, 48 and 72-hour observations) for individual animals were reported: 1.3 and 0.7 for erythema. The mean oedema score (based on 24, 48 and 72 hour observations) was 0 for both animals (REACH n.d.).

Eye irritation

Based on the limited available data, the chemical is considered to cause eye irritation. The observation of corneal opacity in 2 animals that was fully reversible in 7 days, warrants hazard classification as category 2B (see **Hazard classifications relevant for worker health and safety** section).

In a non-GLP, eye irritation study reported to be similar to OECD TG 405, the chemical was instilled into the conjunctival sac of one eye in 2 Vienna white rabbits (sex not reported). The eyes were not washed out, and were observed at 24, 48, 72 hours, and 6 and 7 days. Mean scores (based on 24, 48 and 72 hour observations) for animal 1 were: corneal opacity 2, iritis 0, conjunctiva redness 0.7, and chemosis 0. Mean scores for animal 2 were: corneal opacity 2, iritis 0, conjunctiva redness 1, and chemosis 0. The observed effects were fully reversible within 7 days (REACH n.d.).

Sensitisation

Skin sensitisation

No data are available for the chemical. Based on the read across information, the chemical is not likely to be a skin sensitiser.

In vivo

In a local lymph node assay (LLNA) conducted in accordance with OECD TG 429, female CBA mice (n = 6) received topical applications of a structurally related chemical, NEP at concentrations of 3, 10, or 50% (in acetone). The reported stimulation indices (SI) were 0.99 (3%), 1.01 (10%) and 1.32 (50%). The chemical was not a skin sensitiser (REACH n.d.).

In silico

The chemical has no structural alerts for protein binding based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox v4.5).

Repeat dose toxicity

Oral

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure. There was no clear evidence of specific target organ toxicity in available studies. Observed effects occurred mainly at high doses and were not severe enough to warrant hazard classification based on GHS criteria.

In a GLP compliant 90 day study conducted in accordance with OECD TG 408, Wistar rats (10/sex/dose) were administered the chemical in drinking water at concentrations of 0, 600, 2400, 7200 or 15000 ppm (corresponding to approximately 0, 33–42, 184–230, 529–643 and 1062–1189 mg/kg bw/day). In the 15000 ppm treatment group, the following observations were reported in both sexes: reduced body weight and body weight gain, reduced food and water consumption, increased relative kidney weights decreased serum total protein and globulin concentrations. Increased blood triglyceride concentrations (males), increased urine specific gravity and volume (males), reduced creatinine levels (females), and discoloured urine (males) were also reported. In the 7200 ppm group: decreased body weight, decreased creatinine levels and decreased serum total protein were reported in females. In addition, decreased body weight gain for both sexes and increased relative kidney weights for males were reported. The reported no observed adverse effect level (NOAEL) was 2400 ppm (184–230 mg/kg bw/day) (REACH n.d.).

In a non-guideline 3 month study, female Wistar rats (5/dose) were administered the chemical in drinking water at concentrations of 0, 50 or 15000 ppm (corresponding to 0, 5, and 1339 mg/kg bw/day). In the 15000 ppm group, the following observations were reported: decreased body weight gain, decreased food and water consumption, decreased absolute and relative uterus weight, and increased pituitary gland weight. In the 50 ppm group: decreased body weight gain and decreased food and water consumption, were recorded on fewer days than in the high dose group. Alterations of the thymic cortex were observed in all groups, including the control group. A NOAEL could not be determined (REACH n.d.).

In a non-guideline 14 day study, Wistar rats (3/sex/dose) were administered the chemical in drinking water at concentrations of 0, 8000, 12000 or 15000 ppm (corresponding to 0, 890, 1290, and 1520 mg/kg bw/day). In the 15000 ppm treatment group, the following observations were reported: reduced body weight gain (both sexes), reduced food consumption (females), reduced water consumption (both sexes), and increased relative liver and kidney weights. In the 12000 ppm treatment groups: reduced body weight gain (both sexes), and decreased food and water consumption (females). Decreased food and water

consumption was also observed in females of the 8000 ppm group. The NOAEL was reported to be 12000 ppm (1290 mg/kg bw/day) (REACH n.d.).

In a non-guideline 90 day study, rats and dogs were administered the chemical, in drinking water with no adverse effects reported. Limited study details were available. The reported NOAEL was 100 mg/kg bw/day for rats and dogs (REACH n.d.).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

Based on the available data, the chemical is not likely to be genotoxic.

In vitro

Negative results were reported in the following *in vitro* genotoxicity studies (REACH n.d.):

- In a bacterial reverse mutation assay in *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation at concentrations reported to be up to 165000 µg/plate.
- In an *in vitro* mammalian chromosome aberration assay (OECD TG 473) in human lymphocytes with and without metabolic activation at concentrations up to 6000 µg/mL.
- In an *in vitro* mammalian gene mutation assay (OECD TG 476) in hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary cells with and without metabolic activation at concentrations up to 851 µg/mL.

In vivo

Negative results were reported in the following *in vivo* genotoxicity study (REACH n.d.):

- In a GLP compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, NMRI mice (5/sex/dose) were treated with the chemical by intraperitoneal injection at doses of 0, 500, 1000 or 2000 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (REACH n.d.).

In silico

No structural alerts for mutagenicity or clastogenicity were observed for the chemical and its metabolites (rat liver S9) using the OECD QSAR Toolbox (v4.5).

Carcinogenicity

No data are available for the chemical. Carcinogenicity data are available for the structurally related chemical NMP There is no evidence of carcinogenicity in 2 year studies conducted in rats exposed orally (highest dose 678 mg/kg bw/day) and by inhalation (highest dose 400 mg/m³). There is evidence of liver tumours in mice, although this finding was concluded to be species (B6C3F1) dependent (NICNAS 2013b).

Reproductive and development toxicity

Based on the available data, the chemical may cause specific adverse effects on development, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section).

There is clear evidence of adverse effects on animal development at high doses. The chemical caused high concern malformations in rats and rabbits, with effects in rabbits occurring at the limit dose of 1000 mg/kg bw/day. This included effects on the cardiovascular system which was also identified as a target in rabbit studies with the structurally related substances NMP and NEP (NICNAS 2013b; ECHA 2024). Maternal toxicity was observed in some animals at the doses associated with malformations. However, malformations also occurred in offspring of animals without signs of maternal toxicity, indicating a direct effect of the chemical on development. Therefore, the occurrence of malformations was not associated with maternal toxicity. Classification is also supported by the observed effects of reduced foetal weight in rats and rabbits and an increase in late resorptions in 2 rabbit studies. In the available animal studies, no clear and significant treatment-related effects on female and male reproductive systems, fertility and reproductive outcomes were found.

The ECHA Risk Assessment Committee (RAC) considered whether it was appropriate to set a specific concentration limit (SCL) for the chemical. They calculated an ED10 (effective dose with a 10% effect level above the background) based on the increased incidences of malformations and late resorptions in rabbits. The ED10 values for effects relevant for classification in Category 1B for adverse effects on development were > 400 mg/kg bw/d. On this basis the RAC concluded that 2-pyrrolidone meets the criteria for the low potency group and that an SCL of 3% is warranted.

Sexual function and fertility

In a GLP compliant extended one generation reproductive toxicity study (EOGRTS) conducted in accordance with OECD TG 443, Crl:CD(SD) rats (30/sex/dose) were administered the chemical at concentrations of 0, 1500, 4000 or 8000 ppm in drinking water for 70 days before mating through to the day of euthanasia (the P generation) (ECHA 2023; ECHA 2024; ECHA n.d.). The offspring (the F1 generation) were administered the chemical at concentrations of 0, 1500, 4000 or 8000 ppm in drinking water from weaning until euthanasia (period treated varied for each cohort).

The F1 generation were subdivided into cohorts after weaning and evaluated for the following:

- Cohort 1 for reproductive/developmental toxicity (including oestrous cycles and sperm evaluation),
- Cohort 2 for developmental neurotoxicity (including neurobehaviour, neuropathology and brain morphometry)
- Cohort 3 for immunotoxicity testing.

Male animals receiving the 8000 ppm dose had decreased absolute body weight on day 70 and reduced body weight gain for the whole treatment period. Male animals showed a dose-dependent decrease in both food consumption and food efficiency across all treatment groups. Although female animals receiving the 8000 ppm dose had reduced body weight gain at different treatment periods, the lower body weight at the end of the treatment period was not considered to be statistically significant. Animals of both sexes receiving the 4000 ppm dose also had reduced body weight at different treatment periods, but this was not observed at the end of the treatment period. Any observed organ weight changes (including decreased spleen and thymus weight) were reported to be within historical control ranges and not correlated with any histopathological findings.

There were no substance related effects on any of the reproductive parameters (mating index, fertility index, copulation index, conception index, oestrous cycle length, pre-coital interval and gestation length) in the parental (P) generation.

There is limited evidence of reproductive effects in the F1 generation. A decreased cauda epididymal sperm concentration in males was observed at 8000 ppm (827–853 mg/kg bw/day). The reduced sperm concentration was not correlated with a statistically significant lower cauda epididymis weight. The age of attainment of vaginal patency was delayed in the 8000 ppm dose group which may be related to treatment but also may be a secondary effect of lower body weight.

In a dose range finding study for the reproductive and developmental screening study conducted in accordance with OECD TG 421, Crl:CD(SD) rats (10/sex/dose) were administered the chemical via drinking water at concentrations of 0, 3000, 8000 or 12000 ppm. The P generation was exposed to the chemical from 13 days before mating until the day of euthanasia. For males, this was study day 28 and for females, this was lactation day 21. The selected offspring (F1 generation) was exposed to the chemical from weaning on PND 21 until PND 35 (the day of euthanasia). There were no clear treatment-related effects on reproductive parameters (ECHA 2023; REACH n.d.).

Development

Rabbits

In a GLP compliant prenatal developmental toxicity study conducted in accordance with OECD TG 414, pregnant NZW rabbits (24/dose) were administered the chemical by oral gavage at doses of 0, 250, 500 or 1000 mg/kg bw/day during gestation days (GD) 7–28 (ECHA 2023; ECHA 2024; ECHA n.d.).

The NOAEL for prenatal developmental toxicity was determined to be 250 mg/kg bw/day based on the increased foetal malformations in the 1000 mg/kg bw/day dose group (6% foetuses, 30% litters), increased late resorptions (6%) in the 1000 mg/kg bw/day dose group, and reduced foetal body weight in the 500 and 1000 mg/kg bw/day dose groups (-14.1% and -20% respectively). Malformations in the high dose group were increased above the concurrent and historical control groups. High concern external malformations (ECETOC 2002) including spina bifida and short tail and visceral malformations including effects in the cardiovascular system were reported. Maternal toxicity at high doses included reduced feed consumption and body weight gain. The difference in body weight was less than 10%. An analysis of individual animal data by ECHA showed no relationship between malformations in the foetuses and body weight or food consumption of maternal animals. The 2 animals that were euthanised due to extreme morbidity had viable pups *in utero*.

In a dose range finding study for the prenatal developmental toxicity study, pregnant NZW rabbits (6/dose) were administered the chemical by oral gavage at doses of 0, 100, 300, 700 or 1000 mg/kg bw/day from GD 7–28. An increase in late resorptions (7.9%) was observed in the high dose group and an increase in early resorptions (12.1%) was observed in the group treated with 700 mg/kg bw/day (ECHA 2023; ECHA 2024; ECHA n.d.).

Rats

In a GLP compliant prenatal developmental toxicity study conducted according to OECD TG 414, pregnant SD rats (25/dose) were administered the chemical by gavage at doses of 0, 190, 600 or 1900 mg/kg bw/day from GD 6–15 (ECHA 2023; ECHA 2024; ECHA n.d.). The dosing window in the available study was shorter (GD 6–15) than currently recommended in OECD TG 414 (GD 6–21). The NOAEL for prenatal developmental toxicity was determined to be 600 mg/kg bw/day based on the reduced foetal body weight and increased visceral and skeletal malformations observed in the 1900 mg/kg bw/day dose group. High concern external malformations (ECETOC 2002) including anal atresia, no tail and short tail were statistically significant in the high dose group and were observed in 5 foetuses across 5 litters. The visceral anomalies observed at the high dose included dilatation of lateral ventricles and absent innominate artery. The NOAEL for maternal toxicity was determined to be 600 mg/kg bw/day based on the body weight reduction (-47% corrected body weight change) in the 1900 mg/kg bw/day dose group. In this study, a body weight reduction beyond 10% was reported to be an adverse effect.

In the EOGRTS in Crl:CD(SD) rats (see **Reproductive** section), body weight gain (PND 1–4) was statistically significantly lower in both males and females (F1 generation) in the 4000 and 8000 ppm dose groups. No clear and consistent effects on neurotoxicity were observed in the F1 generation. In F1 females a dose related decrease in number of T- and B-lymphocytes was observed. There were changes in T-cell-dependent antibody response (TDAR), but this did not follow a dose response. Similar to P females decreased spleen and thymus weights were observed. Therefore, changes in TDAR and number of lymphocytes are likely to be more related to general toxicity rather than attributed to *in utero* exposure (ECHA 2023; ECHA 2024; ECHA n.d.).

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