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

Phenol, 2,2'-[(1-methyl-1,2-ethanediyl)bis(nitrilomethylidyne)]bis-

Evaluation statement (EVA00175)

26 June 2025

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AICIS evaluation statement (EVA00175)

Subject of the evaluation

Phenol, 2,2'-[(1-methyl-1,2-ethanediyl)bis(nitrilomethylidyne)]bis-

Chemical in this evaluation

CAS name	CAS number
Phenol, 2,2'-[(1-methyl-1,2-ethanediyl)bis(nitrilomethylidyne)]bis-	94-91-7

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

This 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.

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. Australian Safety Data Sheets (SDS) indicate similar uses to those identified internationally.

Based on international information, the chemical is used as an additive in fuels, and lubricants and greases up to a concentration of 5%. The end use products (e.g. fuel stabilising products) are expected to be used predominantly in commercial applications, with some potential for do it yourself (DIY) use. The chemical may have site-limited functional use as an intermediate in chemical manufacturing.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical.

Based on the available data the chemical:

- has low acute dermal toxicity
- is slightly irritating to the skin or eyes
- is not expected to cause systemic health effects following repeated oral exposure.

The chemical is expected to have moderate acute oral toxicity (median lethal dose (LD50) = 1350 mg/kg in rats).

The chemical is expected to be a skin sensitiser based on *in silico* and *in vivo* data. In 2 independent non-guideline studies in guinea pigs, positive reactions were observed in 90–100% of animals, following topical challenge at 2%.

The chemical is expected to cause reproductive and developmental toxicity, based on 2 *in vivo* guideline studies (OECD TG 422 and OECD TG 421) in rats. The no observed adverse effect level (NOAEL) for reproductive and developmental toxicity is 75 mg/kg body weight (bw)/day, based on reduced gestational index, reduced live litter size, and the incidence of total litter loss. The chemical caused other adverse effects including dam mortality during parturition, dystocia (difficult delivery), pup mortality during lactation, and an increased incidence of pups weighing less than 75% of the mean weight of pups from the control group.

Based on the available data the chemical is not expected to cause point mutations. While an *in vitro* study indicated the potential for clastogenicity, an *in vivo* micronucleus study was negative. However, there was insufficient evidence that the chemical had reached the bone marrow. No data are available for carcinogenicity.

No data are available for inhalation toxicity. Inhalation is not expected to be a relevant route of exposure given the low vapour pressure of the chemical.

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 worker health and safety as follows. This evaluation does not consider classification of physical and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H302: Harmful if swallowed
Skin Sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. 1B	H360FD: May damage fertility; May damage the unborn child

Summary of health risk

Public

Based on the available use information it is unlikely that the public will be exposed to the chemical.

Although the public could come into contact with the chemical during potential DIY uses of products containing the chemical, the expected concentration of the chemical in such products would be low and the duration and frequency of use is expected to be negligible. Therefore, there are no identified risks to the public that require risk management.

Workers

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

Given the critical local and systemic health effects, the chemical could pose a risk to workers. Control measures to minimise dermal exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety (see **Summary of Health Hazards** section).

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 (PCBU) 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 exposure to the chemical include, but are not limited to:

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

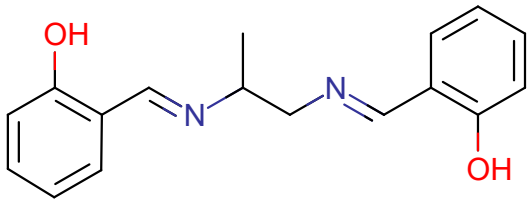
The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

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

CAS number	94-91-7
CAS name	Phenol, 2,2'-[(1-methyl-1,2-ethanediyl)bis(nitrilomethylidyne)]bis-
Molecular formula	$C_{17}H_{18}N_2O_2$
Associated names	*N,N'*-Disalicylidene-1,2-propanediamine 2,2′-[(1-Methyl-1,2-ethanediyl)bis(nitrilomethylidyne)]bis[phenol] *o*-Cresol, α,α′-(propylenedinitrilo)di- α,α'-Propylenedinitrilodi-*o*-cresol
Molecular weight (g/mol)	282.34
SMILES (canonical)	OC=1C=CC=CC1C=NCC(N=CC=2C=CC=CC2O)C
Structural formula	

Relevant physical and chemical properties

The following physico-chemical properties for the chemical were obtained from the CLH report and REACH dossier for the chemical (ECHA 2022; REACH n.d.).

Physical form	Solid
Melting point	53°C
Boiling point	Substance reported to decompose before boiling
Water solubility	190 mg/L
log K_{ow}	3.6 (at 23°C; pH 7)

Introduction and use

Australia

Limited specific Australian information on introduction, use and end use have been identified for the chemical. Use of the chemical in fuel and oil stabilising products at up to 5% concentration has been identified in Australian SDSs.

International

Based on international use information, the chemical has predominantly site-limited and commercial uses. The chemical is used as an additive to fuels and lubricants for cars and aeroplanes, and as a processing aid not otherwise specified (ECHA 2022; REACH n.d.; US EPA n.d.-a; US EPA n.d.-b).

The chemical has reported use in fuel and oil stabilising products (≤ 5%) and fuel anti-gelling products (< 0.2%) (DeLima Associates n.d.; US EPA n.d.-c). These products are expected to be used predominantly in commercial applications, with some potential for DIY use.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is not listed on the HCIS and no specific exposure standards are available in Australia (Safe Work Australia).

International regulatory status

No specific controls have been identified for this chemical.

Health hazard information

Toxicokinetics

There are no toxicokinetic data available for the chemical. Based on its molecular weight, water solubility and log K_{ow} the chemical is expected to be bioavailable via the oral and dermal route. Inhalation is not expected to be a relevant route of exposure given the low vapour pressure of the chemical.

Based on *in silico* modelling, possible chemical biotransformation includes glucuronidation, hydroxylation, sulphonation and hydrolysis (Lhasa Limited n.d.-a). Based on the Organisation

for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Application Toolbox Version 4.5 (OECD 2001), metabolic simulation the chemical is a Schiff base and can be further metabolised to other reactive Schiff bases in skin (OECD 2021).

Acute toxicity

Oral

Based on the available data, the chemical has moderate acute oral toxicity, warranting classification under the GHS (see **Hazard classifications relevant for worker health and safety** section).

In a non-GLP compliant acute oral toxicity study similar to OECD Test Guideline (TG) 401, rats (strain specified as 'US-rats'; 5/sex/dose) were treated with the chemical at doses of 0.2, 1.0, 1.25, 1.6, 2.5, 3.2 or 6.4 mL/kg. The median lethal dose was 1350 mg/kg bw. Reported sublethal signs of toxicity included hunched posture, dyspnoea, aqueous oral secretion, blood encrusted eyes and noses, piloerection, and spastic gait (REACH n.d.).

In 3 other studies in rats with limited study details available, LD50 values of > 1140, 2250 and 4560 mg/kg bw were reported (Chemwatch n.d.; REACH n.d.).

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, Wistar rats (5/sex) were treated with a single 2000 mg/kg bw dose of the chemical. The LD50 was reported to be > 2000 mg/kg bw as no mortality occurred during the study. Slight to well-defined erythema was noted in 3 males (REACH n.d.).

Inhalation

No data are available for the chemical. Inhalation is not expected to be a relevant route of exposure given the low vapour pressure of the chemical.

Corrosion/Irritation

Skin irritation

Based on the weight of evidence, the chemical is considered to be a slight skin irritant. Although the available *in vitro* data indicate that the chemical is a skin irritant, only slight irritant effects were observed in an *in vivo* guideline study. Based on a tiered approach to classification under the GHS, classification is not warranted.

The chemical is considered to be not corrosive in a GLP compliant *in vitro* skin corrosion study conducted in accordance with OECD TG 431. The chemical was applied to reconstructed human epidermis (RhE) for 3 minutes or 1 hour. The mean tissue viability was 100% and 105% after 3 minutes and 1 hour, respectively (REACH n.d.).

The chemical was considered to be at least irritating to skin in a GLP compliant *in vitro* skin irritation study conducted in accordance with OECD TG 439. The chemical was applied to

RhE for an exposure period of 1 hour, followed by an observation period of approximately 42 hours. The resulting mean tissue viability was 10%. Substances that reduce tissue viability to less than 50% in this assay are predicted to be irritants. Interpretation of results obtained from OECD TG 439 studies do not allow for distinction between irritation and corrosion. However, as the test chemical was found to be non-corrosive in the OECD TG 431 study, the chemical is considered to be irritating using the prediction model criteria (REACH n.d.).

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 male New Zealand White rabbits were treated with the chemical for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48 and 72 hours after patch removal. Individual animal scores were not provided. The following mean scores were reported for observation across all time points and animals: 0.53/4 for erythema and 0/4 for oedema. Slight erythema was noted in all animals immediately after removal of the patch, which persisted in 2 animals until 24 hours, and progressed to well-defined erythema in one animal by 24 hours. All reactions were reversed within 72 hours (REACH n.d.).

In a non-guideline skin irritation study, rabbits (2 animals, strain specified as 'white', sex not specified) were treated with the chemical (concentration not specified) for 1, 5, and 15 minutes, and 20 hours, under occlusive conditions. Limited study details were available, but animals were reportedly observed for 8 days, and no signs of erythema or oedema were recorded (REACH n.d.).

Eye irritation

Based on the available data, the chemical is considered to be a slight eye irritant.

In a GLP compliant *in vitro* eye irritation study conducted in accordance with OECD TG 492 (using the EpiOcular™ human cell construct procedure), the chemical was applied to 3-dimensional human cornea model tissue. Cell viability was scored 2 hours after a 30 minute treatment with the chemical (2 tissues per group). The viability of tissues treated with the chemical was determined to be 83%. Based on the prediction model criteria for this assay (mean tissue viability > 60%), the chemical does not require classification for serious eye damage or eye irritation (REACH n.d.).

In a GLP compliant *ex vivo* eye corrosivity/irritation study conducted in accordance with OECD TG 437, the chemical was applied to 3 bovine cornea per experiment. The mean *in vitro* irritancy score (IVIS) was 4. Based on the prediction model criteria, eye irritation potential cannot be concluded for chemicals with IVIS values of > 3 and ≤ 55 (REACH n.d.).

In a non-GLP compliant eye irritation study similar to OECD TG 405, the chemical was instilled into the eye of 2 rabbits (strain specified as 'white', sex not specified). The chemical was not washed out. Ocular reactions were scored at 10 minutes, and at 1, 3, 24, 48 and 72 hours after application. Individual animal scores were not provided. The mean scores (based on observations at 24, 48 and 72 hours) were: corneal opacity 0/4, iritis 0/2, conjunctivae 0.25/3 (fully reversed within 2 days), and chemosis 0/4 (REACH n.d.).

In a non-GLP compliant non-guideline study, the chemical was instilled into the eye of 2 Vienna white rabbits (sex not reported). Ocular reactions were scored at 1, 24, 48 and 72 hours, and animals were observed for up to 8 days. Limited study details were available. Individual animal scores were not provided. The mean scores (based on observations at 24, 48 and 72 hours) were corneal opacity 1/4 (fully reversed within 8 days), iritis 0/2, conjunctivae 0.33/3 (fully reversed within 2 days), and chemosis 0.17/4 (fully reversed within 2 days) (REACH n.d.).

Sensitisation

Skin sensitisation

Based on the available data, the chemical is considered to be a skin sensitiser, warranting classification under the GHS (see **Hazard classifications relevant for worker health and safety** section). As only non-guideline studies are available, sub-classification is not proposed.

In vivo

In a non-GLP compliant, non-guideline guinea pig patch test, 10 guinea pigs (sex and strain not reported) were induced with 20% concentration of the chemical in acetone, by 3 consecutive applications of the chemical to a shaved area of skin on the flank, for 10 consecutive days. The animals were challenged after 11 days with a 2% concentration of the chemical in acetone applied to the opposite, and previously untreated, flank. Approximately 24 hours after challenge, reactions were reported in 90% of the animals. The chemical was reported to be sensitising in this study (REACH n.d.).

In another non-GLP compliant, non-guideline guinea pig patch test, 10 guinea pigs (sex and strain not reported) were treated as per the above study, but with 13 days between the end of the 10 day exposure period and the sensitisation challenge. The animals were challenged with a 2% concentration of the chemical in acetone. Approximately 12 hours after challenge, reactions were reported in 100% of the animals. The chemical was reported to be sensitising in this study (REACH n.d.).

In silico

The parent chemical has no structural alerts for protein binding. Simulated metabolites of the chemical (autoxidation and skin metabolism) have structural alerts for protein binding based on the mechanistic (and endpoint-specific) profiling functionality of the OECD QSAR Toolbox (Version 4.5) (OECD 2001). The chemical alerts are based on the ability of aromatic carbonyl compounds to undergo Schiff base formation and the nucleophilic addition by ketones. These alerts indicate that metabolites of the chemical may have the ability to bind to proteins.

The chemical was out of domain in all skin sensitisation models in OASIS TIMES (LMC 2022) and gave equivocal predictions in and DEREK NEXUS (Lhasa Limited n.d.-b).

Respiratory sensitisation

No data are available for the chemical.

Repeat dose toxicity

Oral

Based on the available data, the chemical is not expected to cause systemic health effects following repeated exposure, beyond those described in the **Reproductive and development toxicity** section.

In a GLP compliant combined repeat dose toxicity study with the reproduction/development toxicity screening test, conducted according to OECD TG 422, Wistar rats (10/sex/dose) were administered the chemical by oral gavage at doses of 0, 25, 75 or 250 mg/kg bw/day.

Males were administered the chemical from 14 days before mating for a total of 29 days, and females were administered the chemical from 14 days before mating, through gestation, and until at least day 4 of lactation, for a total of 42–45 days (see **Reproductive and developmental toxicity** section) (ECHA n.d.; REACH n.d.).

Mortality was observed for 2 animals after dosing on day 9 of the pre-mating period (one female from the 75 mg/kg bw/day group, and one female from the 250 mg/kg bw/day group). These deaths were attributed to complications of gavage, due to gross findings including perforation of the oesophagus, discolouration of the lungs, and fluid in the thoracic cavity. In the 250 mg/kg bw/day group, 2 females were euthanised after total litter loss on day 1 of lactation.

There were no significant changes in body weight, food consumption, haematology, biochemistry, behaviour, organ weights or gross pathology. Histopathological findings included: hyperplasia of the squamous epithelium of the stomach with hyperkeratosis (5/5 females, 6/6 males, 250 mg/kg bw/day), lymphogranulocytic inflammation of the forestomach (2/5 females, 6/6 males, 250 mg/kg bw/day), and thymus lymphoid atrophy (3/5 females, 250 mg/kg bw/day). The NOAEL for the chemical was determined to be 75 mg/kg bw/day, based on histopathological effects observed in animals of the 250 mg/kg bw/day group (ECHA n.d.; REACH n.d.).

In a GLP compliant non-guideline short term repeated dose toxicity study, Wistar rats (4/sex/dose) were administered the chemical by oral gavage at doses of 0, 300, or 800 mg/kg bw/day, for 14 days (n.b. the 800 mg/kg bw/day treatment was discontinued after 4 days due to high toxicity). There were no changes in body weight, or food consumption at 300 mg/kg bw/day. However, there was increased reticulocyte count (both sexes), increased creatinine and inorganic phosphate levels (both sexes), increased urea (females), irregular forestomach surface (3 females, 2 males), and increased absolute and relative organ weights (liver, kidney, adrenal gland; females only). An NOAEL was not reported (REACH n.d.).

Dermal

No data were available for the chemical.

Inhalation

No data were available for the chemical. Inhalation is not expected to be a relevant route of exposure given the low vapour pressure of the chemical.

Genotoxicity

Based on the available data the chemical is not expected to cause point mutations. While an *in vitro* study indicated the potential for clastogenicity, an *in vivo* micronucleus study was negative. However, evidence that the chemical had reached the bone marrow was lacking, therefore, the clastogenicity potential cannot be excluded. Overall, there is insufficient evidence to warrant classification.

In vitro

Negative results were reported in the following *in vitro* genotoxicity studies. A positive result was reported in one mammalian chromosome aberration assay (ECHA n.d.; REACH n.d.):

- Negative results were reported in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* (*S. typhimurium*) TA 1535, TA 1537, TA 98 and TA 100, and in *Escherichia coli* WP2 uvrA, with and without metabolic activation, at concentrations up to 5000 µg/plate.
- Negative results were reported in a bacterial reverse mutation assay (similar to OECD TG 471) in *S. typhimurium* TA 98, TA 7001, TA 7002, TA 7003, TA 7004, TA 7005 and TA 7006, with and without metabolic activation, at concentrations up to 5000 µg/plate.
- Negative results were reported in a mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus in Chinese hamster lung fibroblasts V79, at concentrations up to 176 µg/mL without metabolic activation, and 264 µg/mL with metabolic activation.
- Positive results were reported in a mammalian chromosome aberration assay (OECD TG 473) in Chinese hamster ovary (CHO) cells, with clastogenicity observed at ≥ 22 µg/mL with and without metabolic activation.

In vivo

In a GLP compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, male NMRI mice (treatment group n=7/dose; control groups n=5) received a single administration of the chemical by oral gavage at 0, 500, 1000, or 2000 mg/kg bw day (in polyethylene glycol 400 vehicle). The incidence of micronuclei in bone marrow in erythrocytes did not increase at any dose or testing interval (24 or 48 hours), indicating a lack of clastogenicity. No cytotoxicity was observed in any dose or period of evaluation. Based on available data it cannot be concluded that the chemical reached the bone marrow (ECHA 2023; REACH n.d.).

In silico

The chemical has structural alerts for DNA binding based on the mechanistic and endpoint-specific profiling functionality of the OECD QSAR Toolbox (Version 4.5) (OECD 2001). The chemical has a structural alert for protein binding for chromosome aberrations via Michael-type addition via quinoid structures.

The chemical was out of domain in chromosome aberration models in OASIS TIMES. The chemical was predicted negative for mutagenicity *in vitro* in OASIS TIMES (LMC 2022) and DEREK NEXUS (Lhasa Limited n.d.-b).

Carcinogenicity

No data were available for the chemical.

Reproductive and development toxicity

Based on the available data, the chemical is expected to cause reproductive and developmental toxicity, warranting classification under the GHS (see **Hazard classifications relevant for worker health and safety** section).

There is clear evidence of effects on fertility (dystocia and death during parturition due to inability to deliver) in one guideline study and clear evidence of developmental effects (pup mortality) in 2 guideline studies.

Two GLP compliant test guideline screening studies investigating the reproductive and developmental toxicity of the chemical were performed using the same exposure protocol – dosing 2 weeks before mating, during mating, and for approximately 3 weeks after mating for males and throughout gestation (approximately 3 weeks) and up to postnatal day (PND) 4 for females for a total of 42–45 days (ECHA 2022; REACH n.d.).

In the study conducted according to OECD TG 422, Wistar Crl:WI(Han) rats (10/sex/dose) were orally administered the chemical by gavage at 0, 25, 75 or 250 mg/kg bw/day. In the study similar to OECD TG 421, Wistar Crl:WI(Han)(25/sex/dose) were orally administered by gavage at a single dose of 250 mg/kg bw/day. The OECD 421 study was conducted to investigate the key findings from the OECD 422 study.

In both studies there were no signs of treatment-related general systemic toxicity in males or females.

Sexual function and fertility - females

There were no changes in the following reproductive parameters in either study:

- mating indices
- fertility and conception precoital time indices
- numbers of corpora lutea
- implantation sites.

In the OECD 421 study, the following treatment-related effects were reported for dams exposed to 250 mg/kg bw/day:

- 3 deaths during parturition due to inability to deliver on gestational day (GD) 23. Clinical signs of toxicity observed in 2 animals included apathy, piloerection, and a red/brown vaginal discharge
- one animal had dystocia but survived and delivered healthy pups
- prolonged mean duration of gestation (22.4 compared to 22.0 days for controls).

Effects such as death of dams during delivery and dystocia were not observed in the OECD 422 study. However, based on the lower number of animals per dose group it is not unexpected that effects with low incidences were not observed.

Development

In the OECD 421 study the following treatment-related developmental effects were reported:

- increased number of pups found dead at first litter check (34/219 (15.5%) in the treatment group as compared to 5/259 (1.9%) in the control group)
- reduced viability index (88.0% of pups in the treatment group remained viable between first litter check and PND4, compared to 95.3% in the control group)
- increased number of cannibalised pups (8 in the treatment group compared to 1 control)
- reduced pup body weight; 9% (PND1) and 7% (PND4)
- increased number of runts (pups that weigh less than 75% of the mean weight of pups from the control group) (3 male and 8 females).

In the above analysis the offspring of dams that died during parturition were not considered.

In the OECD 422 study the following developmental effects were reported:

- increase in the number of dead pups at the first litter check (15 in the 250 mg/kg treatment group as compared to 1, 2, and 0 dead pups at 0, 25 and 75 mg/kg bw/d, respectively).
- 2 dams had a total litter loss at the first litter check (decreased gestational index (77.8%) in the 250 mg/kg bw/d group as compared to the other groups (100%))
- decrease in the mean live litter size at 250 mg/kg bw/d as compared with other groups (11.0; 10.2; 12.4 and 8.3 for 0; 25; 75 and 250 mg/kg bw/d, respectively). This analysis excluded dams with total litter loss.

No changes in pup bodyweight or post-natal survival (viability) were observed.

The NOAEL for developmental effects was determined to be 75 mg/kg bw/day.

References

Chemwatch (n.d.), *Galleria Chemica*, Chemwatch website, accessed 1 September 2024.

DeLima Associates (n.d.), *Consumer Product Information Database*, DeLima Associates website, accessed 1 September 2024.

ECHA (European Chemicals Agency) (2022), *CLH report for α,α'-propylenedinitrilodi-o-cresol*, ECHA, accessed 1 September 2024.

Laboratory of Mathematical Chemistry (LMC) (2022), *TIMES (Version 2.31.2)* [Computer software], Laboratory of Mathematical Chemistry, accessed 1 November 2024.

Lhasa Limited (n.d.-a), *Meteor Nexus (Version 3.1.0)* [Computer software], Lhasa Limited, accessed 1 November 2024.Lhasa Limited (n.d.-b) *Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (Version 6.0.1)*, [Computer software], Lhasa Limited, accessed 1 November 2024.

OECD (Organisation for Economic Co-operation and Development) (2021) *Quantitative Structure-Activity Relationship Toolbox (Version 4.5)* [Computer software], OECD, accessed 1 November 2024.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals (n.d.), *Registered dossier for α,α'-propylenedinitrilodi-o-cresol, CAS No. 94-91-7*, REACH website, accessed 1 September 2024.

US EPA (United States Environmental Protection Agency) (n.b.-a), *ChemView database*, US EPA website, accessed 1 November 2024.

US EPA (United States Environmental Protection Agency) (n.d.-b) *CompTox Chemicals Dashboard*, US EPA website, accessed 1 November 2024.

US EPA (United States Environmental Protection Agency) (n.d.-c), *ChemExpo Knowledgebase*, US EPA website, accessed 1 September 2024.