Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Acetic acid, (4-nonylphenoxy)-

Evaluation statement

30 June 2022

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AICIS evaluation statement

Subject of the evaluation

Acetic acid, (4-nonylphenoxy)-

Chemical in this evaluation

Name	CAS registry number
Acetic acid, (4-nonylphenoxy)-	3115-49-9

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is 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 SDS indicate use of the chemical at low concentrations (<1%) in hydraulic fluids, turbine oils.

Based on international information, the chemical is used as a corrosion inhibitor in lubricants and greases, fuels, hydraulic fluids and metal working fluids. The main uses of the chemical are expected to be in commercial and site limited settings. Products may be used by members of the public for car maintenance activities.

Human health

Summary of health hazards

The critical health effects for risk characterisation include local effects (skin corrosion, serious eye damage and skin sensitisation). The chemical has evidence of weak endocrine activity and may be metabolised to nonyl phenol (CAS No. 104-40-5) which is classified for reproductive and developmental toxicity. There was no evidence of reproductive or developmental effects and limited evidence of endocrine effects of the chemical in a combined repeated dose toxicity study with reproduction/developmental toxicity screening test.

The chemical has moderate acute oral toxicity with a median lethal dose (LD50) of 1674 mg/kg bw (REACH). There was insufficient data to determine the acute toxicity of the chemical via dermal and inhalation exposures.

The chemical is considered to be corrosive to skin. Corrosive effects were observed in rabbits exposed to the chemical for 4 hours under semi-occlusive conditions.

The chemical is considered to be corrosive to eyes based on an eye irritation study in rabbits. Instillation of the chemical into rabbit eyes resulted in damage to the cornea and iris, and corrosion of the conjunctiva.

The chemical is considered to be a skin sensitiser based on a guinea pig maximization test (GMPT) in which 75% of test group animals showed skin reactions after challenge with the chemical.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test effects observed at 200 mg/kg bw/day included:

- effects in the thyroid (increased weight and T4 concentrations (both sexes) and minimal diffuse follicular hyperplasia and hypertrophy (females)
- histopathological findings in the stomach (likely due to corrosive effects)
- increased uterine weights.

A no observed adverse effect level (NOAEL) of for oral toxicity 60 mg/kg bw/day was established.

No toxicologically relevant effects on gestation index and duration, parturition, maternal care and early postnatal pup development were observed. The number of live offspring, survival index, sex ratio and gross-pathological findings after birth were not adversely affected by the treatment. The no observed adverse effect level (NOAEL) for fertility and developmental toxicity was 200 mg/kg bw/day.

Based on the available in vitro and in vivo data, the chemical is not expected to be genotoxic.

The chemical exerts mild oestrogenic effects in female rats and anti-androgenic and anti-oestrogenic activity in vitro. In an uterotrophic assay, absolute and relative uterine weights were significantly increased 1.25 and 1.31-fold respectively, at 400 mg/kg bw. In the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test high dose females (200 mg kg/bw/day) had significantly increased relative uterine weights compared to controls but no histopathological changes were observed. There were no organ weight or histopathological findings in the ovaries, epididymides, prostate and seminal vesicles. There are currently no established adverse outcome pathways for weak oestrogenic activity.

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
Acute Toxicity	Acute Tox. 4	H302: Harmful if swallowed.
Skin Corrosion	Skin Corr. 1	H314: Causes severe skin burns and eye damage.
Eye Damage	Eye Dam. 1	H318: Causes serious eye damage.
Skin Sensitisation	Skin Sen. 1A	H317: May cause an allergic skin reaction.

Summary of health risk

Public

Based on the available use information, the most significant source of public exposure will be through using auto products during car maintenance activities. Therefore, widespread public exposure is not expected, with exposure limited to hobbyists. Members of the public that undertake car maintenance activities may be exposed to the chemical at concentrations up to 1% by incidental skin and eye contact during use of products. The concentration level at which the public will be exposed is unlikely to cause local effects. Auto products available to consumers are also expected to be available in the workplace, and subject to workplace labelling. Workplace labelling will identify the hazards of any products containing the chemical. Therefore, there are no identified risks to the public that require 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 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 critical local health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and ocular exposure are needed to manage the risk to workers (see **Proposed means for managing risks section**). Control measures implemented due to the corrosivity classification are expected to be sufficient to protect workers from any potential systemic health effects.

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 new classifications relevant to work health and safety.

Information on managing identified risks

The information in this report includes recommended hazard classifications and 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 Model Work Health and Safety Regulations.

Control measures that could be implemented to manage the risk arising from exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes or conducting work tasks through automated processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using personal protective equipment (PPE) that is designed, constructed and operated to ensure that workers do not come into contact with the chemical.

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.

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.

PPE should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures cannot eliminate or sufficiently minimise risk. Guidance in selecting PPE can be obtained from Australian, Australian/New Zealand or other approved standards.

Model codes of practice, available from the Safe Work Australia, 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

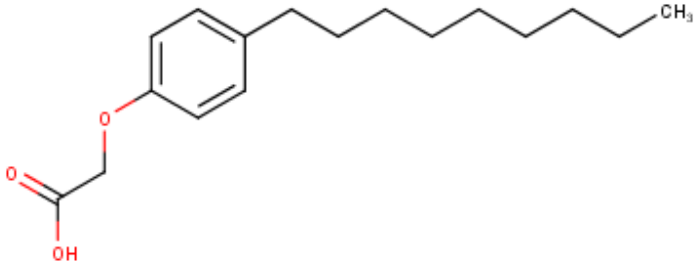
The conclusions of this evaluation are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

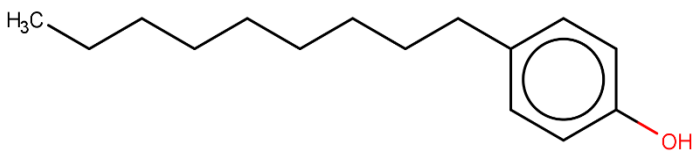
Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	Acetic acid, (4-nonylphenoxy)-
CAS No.	3115-49-9
Synonyms	acetic acid, (p-nonylphenoxy)- acetic acid, (4-nonylphenoxy)- (p-nonylphenoxy)acetic acid 4-nonylphenoxyacetic acid
Structural formula	
Molecular formula	C17H26O3
Molecular weight (g/mol)	278.4
SMILES	O=C(O)COC1=CC=C(C=C1)CCCCCCCCC
Chemical description	Whilst the substitution pattern and branching structure of the alkyl chain is not specified, in technical nonylphenol mixtures, branched para-nonylphenol isomers constitute at least 90 % of the final product

Chemical identity information for related chemicals

Chemical name	Phenol, 4-nonyl
CAS No.	104-40-5
Synonyms	4-nonylphenol p-nonylphenol
Structural formula	
Molecular formula	C15H24O

Molecular weight (g/mol)	220.4
SMILES	OC1=CC=C(C=C1)CCCCCCCCC
Chemical description	-

Relevant physical and chemical properties

Physical form	Liquid
Melting point	<25 °C
Boiling point	406.8 ± 20.0 °C (predicted)
Vapour pressure	0.0025 Pa at 25 °C
Water solubility	0.04 mg/L
Henry's law constant	N/A
Ionisable in the environment?	No
pKa	3.1 at 25 °C
log K_{ow}	5.8 (predicted for undissociated form) and with a log Kow of 3.6 at pH5.

Introduction and use

Australia

Limited specific information is available about the introduction, use and end use of the chemical in Australia. Australian SDS indicating use of the chemical at low concentrations (<1%) in hydraulic fluids, turbine oils

International

The following international uses have been identified through Galleria Chemica, the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers, and the Substances and Preparations in Nordic countries (SPIN) database.

The chemical has reported commercial and domestic use as a corrosion inhibitor or viscosity adjustor in:

- hydraulic fluids and additives
- lubricants and greases
- fuels
- metal working fluids.

Under the US Toxic Substances Control Act (US EPA 2016) Chemical Data Reporting (CDR) rule, the chemical was reported to be used in lubricants and greases at a minimum concentration of 1% but less than 30% by weight.

These products may be used by members of the public for car maintenance activities.

The chemical has reported site limited uses in the manufacture of chemicals.

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 Hazardous Chemical Information System (HCIS) and no exposure standards are available for the chemical in Australia (SWA).

International Regulatory Status

Canada

The chemical has the following significant new activity (SNAc) order under the authority of the Canadian Environmental Protection Act, 1999 (CEPA) (Canada 2017):

- 'Any activity that does not include the substance being used as a corrosion inhibitor and metal deactivator for use in industrial lubricant additives.'

Health hazard information

Toxicokinetics

No toxicokinetic studies are available for the chemical. The chemical has a low molecular weight (278.4 g/mol) with a calculated log K_{ow} value of 5.8 which is pH dependent. It is expected to be bioavailable following oral and dermal administration. Flux values of 19, 0.5, 0.3 and 0.56 µg/cm^2 and 1hr were calculated for a saturated aqueous solution of (4-nonylphenoxy)-acetic acid with a log K_{ow} of 3.6 and a pH of 5 (Hartwig A 2021). The chemical has low volatility and; therefore, the inhalation route is not expected to be a route of exposure.

The chemical is expected to metabolise to nonylphenol (CAS No. 104-40-5) in the body and in the environment, similarly to the related nonylphenol ethoxylates (NICNAS 2019b). The OECD QSAR Toolbox (rat liver S9 metabolism simulator) predicted the formation of nonylphenol as well as other metabolites (OECD, 2022).

Nonylphenol is rapidly absorbed via the gastrointestinal tract and undergo extensive first-pass metabolism. The major metabolic pathways for nonylphenols are via glucuronide and sulfate conjugation (NICNAS 2019a).

Acute toxicity

Oral

Based on the available data, the chemical has moderate acute oral toxicity, which warrants hazard classification.

In a good laboratory practice (GLP)-compliant acute oral toxicity study conducted in accordance with the OECD TG 401, the chemical was administered to Wistar rats (5/sex) by oral gavage at 1000, 2000, 3000 or 5000 mg/kg bw. Mortality was observed at 2000 mg/kg bw (3/5 males and 3/5 females). No animals survived at 3000 mg/kg bw and above. Reported signs of toxicity included sedation, rales, dyspnoea (laboured breathing), ataxia (impaired coordination), curved body position and ruffled fur. In females, laying on the front or side, chromodaccryorrhea (bloody tears) and muscle twitching were observed. The reported LD50 was 1674 mg/kg bw in rats (REACH).

Corrosion

Skin irritation

Based on the available data, the chemical is considered corrosive to skin and warrants hazard classification.

In a non-GLP compliant skin irritation study conducted in accordance with OECD TG 404, 0.5 mL of the chemical was applied to the skin of 3 female New Zealand White (NZW) rabbits for 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48, and 72 hours after patch removal. Erythema and oedema each with a score of 2 was observed in all animals after 1 hour. The mean scores following grading at 24, 48 and 72 hours for individual animals were 3.3, 3.7 and 3.7 for erythema and 3 for all three animals for oedema. Scores consistent with corrosive effects were reported in all animals after 48 hours. The observed effects were not reversible within 72 hours after which the study was discontinued (REACH).

Eye irritation

Based on the available data, the chemical cause serious eye damage and warrants hazard classification.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, 0.1 mL of the chemical was instilled into one eye of 3 male NZW rabbits which were observed at 1, 24, 48 and 72 hours. The eyes reacted with spontaneous swellings and hyperaemia upon instillation of the test substance. The mean scores following grading at 24, 48 and 72 hours for the 3 individual animals were: 2.3, 2.7, and 2.7 for corneal opacity; 2, 1.7 and 1.7 for iritis; 2.7, 3, and 3 for conjunctival redness; and 3.3, 4 and 4 for chemosis. The observed effects were not reversible within 72 hours after which the study was discontinued (REACH).

Sensitisation

Skin sensitisation

Based on the available data, the chemical is considered to be a skin sensitiser and warrants hazard classification.

In a non-GLP compliant GPMT conducted according to OECD TG 406, intradermal induction was performed on 20 female Pirbright White Guinea Pigs using 1% of the chemical (commercial grade) in sesame oil and topical induction with 3% of the chemical in petrolatum. The animals were challenged with 0.3% of the chemical in petrolatum. After challenge, reactions were reported in 15 out of 20 animals (75%) of the animals (REACH).

The chemical has structural alerts for protein binding based on the mechanistic profiling functionality of the OECD QSAR Toolbox v4.2 (OECD 2022). The QSAR modelling using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue MEtabolism Simulator; version 2.28.1.6) predicted positive results (in domain) for skin sensitisation (mechanistic alert: alpha-activated acetates) for the chemicals.

Repeat dose toxicity

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure. Effects in the thyroid reported at 200 mg/kg bw/day are considered not to warrant hazard classification.

Oral

In a GLP compliant combined repeated oral toxicity and reproductive toxicity study conducted in accordance with OECD TG 422, WI(Han) rats (outbred) (10/sex/dose) were administered the chemical via oral gavage at doses of 20, 60, or 200 mg/kg bw/day. The males were exposed for a total of 29 days and females were exposed for a total of 43 to 56 days.

No mortality occurred during the study. At 200 mg/kg bw/day, reduced body weight gain and increased liver and thyroid weights were observed in both sexes. T4 concentrations were increased in both sexes at the highest dose. Histopathological findings were reported in the stomach in both sexes; however, these effects are likely to be due to the corrosive nature of the chemical. At 200 mg/kg bw/day minimal diffuse follicular hyperplasia and hypertrophy was observed in in thyroids of females. Hearing ability, pupillary reflex, static righting reflex and grip strength were unchanged by exposure to the chemical. The NOAEL was determined to be 60 mg/kg bw/day based on the effect on body weight, organ weights and histopathology at 200 mg/kg bw/day (Hartwig 2021; REACH).

In a range-finding study conducted in Wistar Han rats (Crl:WI(Han)) (4/sex/dose) were exposed to the chemical (purity 97.4%) at dose levels of 0, 150 or 450 mg/kg bw/day for 14 days. Testing was discontinued in the 450 mg/kg bw/day group after 7 days due to severe toxicity. At the end of the treatment period (days 10 and 14), the body weight gains in the females receiving 150 mg/kg bw/day were slightly lower. Glucose levels were increased in males. Alanine aminotransferase and alkaline phosphatase activities were increased in females. Relative liver weights were slightly increased in the animals at 150 mg/kg. In the majority of animals, the forestomach was found to have an irregular surface, while a few had gelatinous contents in the gastrointestinal tract and isolated dark red foci on the stomach glandular mucosa (Hartwig 2021).

Genotoxicity

Negative results were reported in the following in vitro genotoxicity studies:

- In a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100 with and without metabolic activation at concentrations up to 5120 µg/plate.
- In a mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus in Chinese hamster lung cells V79 with and without metabolic activation at concentrations up to 44.0 µg/mL.

In a non-GLP compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, Chinese hamsters (6/sex/dose) were treated with the chemical by oral gavage at single doses of 1000, 2000, or 4000 mg/kg bw. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (REACH).

Carcinogenicity

No data are available for the chemical.

Reproductive and development toxicity

Based on the available data, the chemical is not expected to cause specific adverse effects on development or fertility following repeated or prolonged exposure. However, the chemical may metabolise to nonylphenol which classified for reproductive and developmental toxicity based on animal data (NICNAS 2019a).

In a repeated dose toxicity study with reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, animals were administered the chemical by oral gavage once daily from 14 days before mating for a total of 29 days in males, and before mating, during mating, post-coitum, and during at least 4 days of lactation (up to the day prior to scheduled necropsy) for a total of 43–56 days in females (see **Repeat dose toxicity**). No toxicologically relevant effects on reproductive parameters were reported. Mating, fertility and conception indices, pre-coital time, and the number of corpora lutea and implantation sites were unaffected by the treatment. The number of live offspring, survival index, sex ratio and gross pathological findings after birth were not adversely affected by the treatment. High dose females had significantly increased relative uterine weights compared to control animals but no histopathological changes were observed. There were no organ weight or histopathological findings in the ovaries, epididymides, prostate and seminal vesicles. Effects on anogenital distance (AGD) and oestrus cycle do not appear to have been measured in this study. The no observed adverse effect level (NOAEL) for fertility and developmental toxicity was 200 mg/kg bw/day (Hartwig 2021; REACH).

Reproductive and developmental toxicity studies with nonylphenol have reported reproductive effects in male rats (decreased epididymal sperm density and testicular spermatid head counts) and in female rats (increased oestrus cycle length and decreased ovarian weights) when exposed to nonylphenol (NICNAS 2019a). Further developmental studies are required to determine whether nonylphenoxyacetic acid have similar effects on the male reproductive systems as nonylphenol.

Endocrine effects

In a uterotrophic assay, rats were administered the chemical at 100, 200, 300 or 400 mg/kg bw/day for 3 days. As a positive control, a group of animals received oestradiol benzoate (0.5 µg/animal) subcutaneously. Bodyweight was significantly reduced in the 200, 300 and 400 mg/kg bw/day dose groups to 79%, 56%, and 63% relative to the vehicle control, respectively. At 400 mg/kg the absolute and relative uterine weight were significantly increased by 1.25-fold and 1.31-fold respectively relative to the vehicle control group compared to 3.76-fold and 3.82-fold with the positive control. These results indicate that the chemical may have weak oestrogenic activity; however, there are no established adverse outcome pathways for weak oestrogenic activity. No other treatment related effects on clinical signs of toxicity were reported (Hartwig 2021).

In a non-GLP compliant in vitro yeast androgen screening assay to determine androgenic and antiandrogenic potential, the chemical showed no androgenic activity in comparison to dihydrotestosterone and clear antiandrogenic activity at 10^{-5} mol/L and above in comparison to hydroxyflutamide. No cytotoxicity was observed (REACH).

In an in vitro yeast oestrogen screening assay with the human oestrogen receptor and β-galactosidase reporter gene, the chemical showed no oestrogenic activity compared with 17β-oestradiol, but slight anti-oestrogenic activity at 10–5 mol/l and above compared with hydroxytamoxifen. No cytotoxicity was observed (Hartwig 2021)

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