Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Nonanedioic acid (azelaic acid)

Evaluation statement

14 September 2021

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Nonanedioic acid (azelaic acid)

Chemical in this evaluation

Name	CAS registry number
Nonanedioic acid	123-99-9

Reason for the evaluation

An evaluation is required to provide information on the risks to human health.

Parameters of evaluation

Nonanedioic acid is listed on the Australian Inventory of Industrial Chemicals (the Inventory); it is often referred to by its common synonym of azelaic acid. This evaluation will focus on determining whether the identified health hazards are appropriately risk-managed for the range of reported industrial uses of the chemical.

It should be noted that nonanedioic acid is used topically as a therapeutic good (TGA 2021). As this is an excluded use it is not considered in this evaluation.

Summary of evaluation

Summary of introduction, use and end use

There is no available information on industrial use of the chemical in Australia. The chemical is reported to have domestic and commercial uses overseas, such as in cleaning and washing products, greases, leather treatment products, putties, waxes, inks and toners. The chemical is also reported to be used to manufacture a type of nylon (nylon 69), which is used in plastic articles, and it is a constituent of a number of polyesters. While there are cosmetic uses reported overseas, these are considered excluded uses in Australia, due to the therapeutic mode of action determined for nonanedioic acid (TGA 2021).

Human health

Summary of health hazards

The critical health effects for risk characterisation include skin and eye irritation. Skin and eye irritation effects have been reported in both animal studies and human observations (see supporting information).

The chemical has very low acute oral and dermal toxicity. It is not a skin sensitiser, not genotoxic, and does not result in reproductive or developmental toxicity. The chemical is also not expected to be carcinogenic.

Further details on the evaluation of these health hazards is provided in the section 'Supporting Information' (see below).

Health hazard classification

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 and environmental hazards.

Health hazards	Hazard category	Hazard statement
Skin irritation	Category 2	H315: Causes skin irritation
Eye irritation	Category 2	H320: Causes eye irritation

Summary of health risk

Public

Current regulatory controls in Australia only allows the sale and supply of pharmacy products or prescription medicines containing nonanedioic acid, with an exemption for non-human use at <1% concentration (refer to Supporting information section). Although no Australian-specific use information is available, the chemical is reported internationally to be present in consumer products (domestic use). Incidental dermal and ocular exposure may occur from using these products. However, based on the available hazard information (skin and eye irritation), there are no identified risks to the public that require management, where use of the chemical as a dermal or topical application is not intentional.

Workers

During product formulation and packaging, dermal, 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.

Given the critical local health effects of skin and eye irritation, the chemical could pose a risk to workers. Control measures to minimise dermal and ocular exposure are needed to manage the risk to workers (refer to **Recommendation** section).

Conclusions

The conclusions of this evaluation are based on the information described in the statement. Obligations to report additional information about hazards under section 100 of the IC Act apply.

The Executive Director is satisfied that the identified human health risks can be managed within the 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. The proposed means of managing the risks identified during this evaluation are set out in the Recommendations section.

Recommendations

Public health

It is recommended that the delegate of the Secretary for Poisons Scheduling amends the entry in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP).

Consideration should be given to the following:

- the range of identified industrial uses of the chemical, for which dermal or topical application is not intentional
- the schedule entries do not explicitly exclude derivatives, of which a large number are found on the Inventory
- the identified health hazards of the chemical being limited to local effects of skin and eye irritation
- current scheduling limits the maximum use concentration of the chemical to <1%, even where intended use is not dermal or topical application.

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the HCIS to include classifications relevant to work health and safety.

Advice to industry

The information in this report, 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.

Recommended control measures that could be implemented to manage the risk arising from exposure to these chemicals include, but are not limited to:

- 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 chemicals.

Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemicals depend on the physical form and the manner in which the chemicals are used.

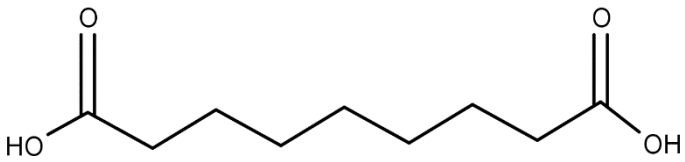
Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

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.

Supporting information

Chemical identity

Azelaic acid is a saturated 9-carbon length dicarboxylic acid that owes its name to the fact that it was originally obtained from the oxidation of oleic acid by nitric acid. In addition, it can also be obtained by fermentation by a variety of microorganisms such as *Brettanomyces petrophilum*.

Synonyms	azelaic acid; 1,7-dicarboxyheptane; 1,7-heptanedicarboxylic acid; anchoic acid; lepargylic acid; 1,9-nonanedioic acid
Structural formula	
Molecular formula	$C_9H_{16}O_4$
Molecular weight (g/mol)	188.22
SMILES	O=C(O)CCCCCCCC(=O)O
Chemical description	White solid, organic compound

Relevant physical and chemical properties

Physical form	White powder

Melting point	106.5 °C
Boiling point	286.5 °C
Vapour pressure	1.44 x 10^{-6} Pa at 25 °C
Water solubility	2.4 g/L at 20 °C
pKa	4.55 at 25 °C
log K_{ow}	1.57

Introduction and use

Australia

No information is available on the industrial use of the chemical in Australia.

International

While topical use of nonanedioic acid in Australia is considered an AICIS-excluded use due to the determined therapeutic mode of action, it is noted that the chemical is available for use internationally as a cosmetic. Reported functions include use as a buffering agent and fragrance (COSING). Other reported cosmetic uses include as an antimicrobial and anti-acne agent (Personal Care Products Council), in personal care products (ECHA REACH a), skin serums, lotions, gel masks, creams, shampoos and exfoliants (used for acne and rosacea), skin-whitening/brightening and to promote hair growth (Fiume et al 2012).

Nonanedioic acid is listed on the 2004 Organisation for Economic Cooperation and Development (OECD) List of High Production Volume Chemicals. This substance was produced at a level greater than 1000 tons per year in at least one member country of the European Union (EU).

The following international industrial uses were identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Substances and Preparations in Nordic countries (SPIN) database; and other international reports and sources of information (Sastri 2010).

The chemical has reported domestic use in:

- washing and cleaning products
- polishes and waxes
- fillers, putties, plasters and modelling clay
- inks, toners, paints, lacquers and varnishes.

The chemical has reported commercial uses including in:

- the manufacture of fabricated metal products, machinery, equipment, transport equipment, and in construction materials
- lubricants, greases and cutting fluids
- additives, hardeners and process regulators

- leather treatment products.

The chemical is also reported to be used in the preparation of nylon (69 resins), which is used in plastic articles, and it is a constituent of a number of polyesters.

Existing Australian regulatory controls

AICIS

There are no AICIS specific regulatory controls applicable to this chemical.

Public

Azelaic acid is listed in the Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Schedules 2 and 4.

Schedule 2:

'AZELAIC ACID in dermal preparations.'

Schedule 4:

'AZELAIC ACID **except**:

a) when included in Schedule 2; or
b) in preparations containing 1 per cent or less of azelaic acid for non-human use.'

Schedule 2 chemicals are described as 'Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person.' Schedule 2 chemicals are labelled with 'Pharmacy Medicine'.

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.' Schedule 4 chemicals are labelled with 'Prescription Only Medicine' or 'Prescription Animal Remedy' (SUSMP 2021).

Workers

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

International regulatory status

Exposure standards

No specific exposure standards are available for the chemical.

Asia

The chemical is listed in the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II, Part 1 – List of substances which must not form part of the composition of cosmetic products (ASEAN 2020).

Health hazard information

Acute toxicity

Oral

A number of acute oral toxicity studies in animals are available. While limited study details are available, based on the weight of evidence, the chemical is considered to have low acute oral toxicity.

Following single oral (gavage) doses of azelaic acid administered as a suspension, the reported minimum lethal doses were 3750 mg/kg bw (male mice) and 5000 mg/kg bw (female mice and male rats). Clinical signs observed included accelerated respiration (rats). Mortalities occurred within 1.5 to 3 days after oral administration (US FDA 2015).

In a non-guideline acute oral toxicity study with limited study details, 2 Sprague Dawley (SD) male rats were orally administered azelaic acid (vehicle unspecified) at 5000 mg/kg bw. No mortalities were reported. No other doses were tested. The LD50 in SD rats was >5000 mg/kg bw (ECHA REACH a; OECD SIAR 2014).

In a non-guideline acute oral toxicity study with limited study details, an 80% azelaic acid formulation (Emerox® 1110) was administered by stomach tube to male albino rabbits (5 animals/dose group) at doses of 215 and 10000 mg/kg bw. No mortalities were reported. Average body weight gains were within normal limits. Gross autopsy showed no significant pathological findings in any dose groups (CDC 1977).

Following single oral (gavage) doses of azelaic acid in dogs, at doses of ≥250 mg/kg bw as a suspension, emesis was observed immediately up to 4.5 hours. Diarrhoea also occurred 2.5 to 3.5 hours after dosing at a dose level of 5000 mg/kg bw. No mortalities were reported (US FDA 2015).

Dermal

Based on the weight of evidence from available information, including skin irritation studies in animals and humans (refer to Skin irritation section), the chemical is expected to have low acute dermal toxicity.

In an acute dermal toxicity study with limited study details, a commercial formulation (Emerox® 1110) containing 80% azelaic acid in a 50% w/v suspension in water, was applied to the skin of albino rabbits (4 animals/dose group) at 1000, 2200, 4600 and 10000 mg/kg bw. A single mortality was observed at the dose of 4600 mg/kg bw, which was reported to be due to acute enteritis. Mild or moderate erythema was observed in a few animals for 1 to 4 days. The LD50 was reported to be >2000 mg/kg bw (CDC 1977).

In a 7 day dermal exposure study, azelaic acid (15% and 30% in a pre-foam emulsion formulation) was applied to 10% of the body surface area of intact mouse skin at doses of 0,

1500 and 3000 mg/kg bw/day at 5 mL/kg bw twice-daily, at 8-hour intervals. One male at the highest dose (3000 mg/kg bw/day) was found deceased on day 7. No signs of systemic toxicity or other mortalities were noted. No treatment related dermal irritation, effects on body weight, food consumption or macroscopic findings were noted in this study (US FDA 2015).

Inhalation

Inhalation of azelaic acid as vapour is not expected due to its low vapour pressure (see Relevant physical and chemical properties section).

Corrosion/Irritation

Skin irritation

Based on the weight of evidence, the chemical is considered to be a skin irritant. Effects have been reported in both animal and human studies (refer to Observations in humans below). There is sufficient evidence to warrant hazard classification as 'Skin irritation – Category 2.

Two gel formulations and one pre-foam emulsion of 15% azelaic acid (500 mg) was topically applied to intact shaved skin of 1 male and 2 female New Zealand White (NZW) rabbits (4 sites/animal; 6 cm^2/site) under semi-occlusive conditions, for 5 hours. Each treatment site was evaluated for signs of dermal irritation immediately after patch removal and at 24, 48 and 72 hours post-patch removal. All formulations of the chemical were reported to be "mild irritants" under the conditions of this study. Total reversibility was noted at 48 hours for both 15% azelaic acid gel formulations, and at 72 hours for the 15% azelaic acid pre-foam emulsion (US FDA 2015).

In a non-guideline study, the primary skin irritation potential of azelaic acid (0.5 g for solids and 0.5 mL for liquids) was tested by a patch test technique (limited details available) under occlusive conditions on intact and abraded skin areas of 6 NZW rabbits. Abrasions were minor incisions through the stratum corneum, reported as not deep enough to disturb the derma or to produce bleeding. The test substance was applied for 24 hours and animals were observed for 72 hours. No signs of erythema or oedema were observed in the study (ECHA REACHa).

Eye irritation

Based on the weight of evidence, the chemical is considered to cause eye irritation. Effects have been reported in both animal studies and human observations (refer to Observations in humans below). There is sufficient evidence to warrant hazard classification of the chemical as 'Eye Irritation – Category 2'.

A formulation of 20% azelaic acid cream (reported as preservative-free) or vehicle (0.1 mL) was applied to the eyes of rabbits (number not specified). Moderate to severe ocular irritation was noted (no scoring provided) after application of the cream formulation, with signs of reddening, swelling, erosion of the cornea, secretion, eyelid closure and necrosis of parts of conjunctivae. Only slight irritation was noted in the vehicle control group (US FDA 2015).

A single application of 20% azelaic acid cream (40 mg) was applied to the eyes of monkeys (number not specified) and rinsed at 30 seconds after application. Pain reactions were noted immediately after application and disappeared after rinsing. Local effects observed included reddening, swelling and vessel injections of conjunctivae despite rinsing. These effects were

reported to be reversible after 1 to 4 days. Only slight irritation was reported following application of the vehicle alone (US FDA 2015).

Respiratory irritation

While inhalation of azelaic acid as vapour is not expected due to its low vapour pressure (see Relevant physical and chemical properties section), respiratory irritation has been reported in humans exposed to airborne particles (refer to Observation in humans below). However, confounding factors such as exposure to other chemicals could not be completely ruled out for these observations.

Observation in humans

A single-centre, controlled, investigator-blinded study compared the cumulative irritation potential of rosacea treatments, including a 15% azelaic acid gel formulation. While no specific study methods are available, it is reported that on the last day of the study (day 22), all 32 subjects experienced erythematic skin reactions with the 15% azelaic acid gel, with 59.4% of reactions reported as severe. Other reactions, reported as non-erythematic, were 10 accounts of blisters, 8 observations of oedema, 3 accounts of vesiculation, and 2 observations of weeping/oozing, all of which occurred with the 15% azelaic acid gel. A total of 51 adverse events were reported in response to 15% azelaic acid, during the course of this study (Colon et al 2007).

In another study, the cumulative potential of 15% azelaic acid gel formulation was evaluated in 31 females and 2 males (1 withdrew for personal reasons). Participants were patch tested (under occlusion) with 0.2 g of azelaic acid or a negative control (petrolatum) 3 times per week for 3 weeks. The azelaic acid gel was found to be more irritating compared with the negative control. Individual reaction scores ranged from 0 to 3. Five participants discontinued due to an irritation score ≥3. Cumulative irritancy increased with successive patching. It is reported that the vehicle used for azelaic acid was not tested; therefore, uncertainty exists as to whether the vehicle components affected the irritation scores (Fiume et al 2012).

In the US, workers at a factory that produced Emerox® solid flake products containing 80–90% azelaic acid were exposed to airborne particles of azelaic acid in the range of 0.1–3.8 mg/m^3 and carbon monoxide. Workers reported irritation of the skin, erythema around the wrists and on the face, burning of the eyes, irritation of the nose and the upper respiratory tract resulting in increased nasal secretions, nose bleed, sneezing and nasal burning, all of which were of short duration and made more severe during hot weather. Slight erythema of the nasal mucosa was observed in one worker involved in bagging Emerox® (CDC 1977). However, confounding factors such as exposure to other chemicals could not be completely ruled out with these observations.

Sensitisation

Skin sensitisation

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

In a guinea pig maximisation test (GPMT) conducted according to OECD Test Guideline (TG) 406, Pirbright white guinea pigs (20/sex/dose) received 0.5% (w/v) azelaic acid (in NaCl and water) by intradermal injection for induction. On day 9, this was followed by topical application of 25% (w/v) azelaic acid (in NaCl and water) for 48 hours under occlusion. On day 22, animals were challenged with 15% (w/v) azelaic acid (in paraffin oil) topically under

occlusion for 24 hours. Observations were made at 24 and 48 hours after removal of the occlusive bandage. No reactions were observed following challenge. Azelaic acid was not sensitising to the skin based on the study results (ECHA REACHa).

In a non-guideline GPMT similar to OECD TG 406, with limited study details, Dunkin Hartley guinea pigs (5/sex) received 0.25% azelaic acid (in acetone/PEG400) by intradermal injection for induction, followed by topical application of 50% azelaic acid (in acetone/PEG400) under occlusion. Animals were challenged with 50% azelaic acid (in acetone/PEG400) topically under occlusion. No reactions were observed during the study. Azelaic acid was not considered to be sensitising to the skin in this study (ECHA REACHa).

In another GPMT, 0.5% azelaic acid was used for intradermal induction. All animals were treated with 10% sodium lauryl sulfate on the day prior to topical induction. Topical induction used a single dose of 25% azelaic acid (aqueous suspension, 0.2 mL. For the challenge phase, a single dose of 15% azelaic acid (oil suspension, 0.1 mL) was applied topically to the flank on day 22 and occluded for 24 hours. No skin reactions were observed following challenge (US FDA 2015).

In a local lymph node assay (LLNA) in mice, 25 µL of a 15% azelaic acid pre-foam emulsion, or vehicle, was applied daily over the entire dorsal surface of each ear for 3 days. Only limited details are available; however, no lymphocyte proliferation and no treatment-related effects on ear weights were reported under the conditions of this study (US FDA 2015).

Repeat dose toxicity

Oral

Based on the limited available information, the chemical is not expected to cause serious systemic health effects following repeated oral exposure.

Azelaic acid was orally (gavage) administered as a daily suspension at doses of 0, 100 and 1000 mg/kg bw/day to male and female rats for 27 weeks. At 1000 mg/kg bw/day, lower body weight gain and slightly higher water consumption compared to the control group were observed. Slightly lower food consumption and thickening of the cuticular ridge of the stomach were observed in both dose groups accompanied by evagination and epithelial overgrowth in the high dose group. The reported NOAEL was 100 mg/kg bw/day (US FDA 2015).

Azelaic acid was orally (gavage) administered as a daily suspension at doses of 0 and 250 mg/kg bw/day to monkeys for 4 weeks. The dose for this study was selected to avoid monkeys vomiting. No treatment related effects were observed in this study (US FDA 2015).

Azelaic acid in gelatin capsules was orally (gavage) administered at doses of 0, 10, 100 and 800 mg/kg bw/day to dogs for 6 months, with a 1 month recovery period. No treatment related effects were observed in this study. The reported NOAEL was 800 mg/kg bw/day (US FDA 2015).

Dermal

Based on the limited available information, the chemical is not expected to cause serious systemic health effects following repeated dermal exposure.

In a repeated dermal toxicity study, 20% azelaic acid cream was applied dermally at doses of 0, 50, 100 and 300 mg/kg bw/day on a daily basis to rats for 6 months, with a 1 month recovery period. No treatment related effects were observed in the study. The reported NOAEL was 300 mg/kg bw/day (US FDA 2015).

A 20% azelaic acid cream at doses of 0 (vehicle) and 300 mg/kg bw/day was dermally applied (under occlusive dressing for 24 hours after dosing) to dogs for 26 weeks. No treatment related systemic effects were noted in this study. In the 300 mg/kg bw/day group, slight irritation at the application site was observed more frequently compared with the control group. The reported NOAEL was 300 mg/kg bw/day (reported as the maximum feasible dose) (US FDA 2015).

Dermal doses of 0 (untreated control or vehicle), 75, 225 and 450 mg/kg bw/day azelaic acid (5, 15, and 30% emulsion applied to 10% body surface area at 0.75 mL/kg/dose twice daily) were applied to minipigs for 13 weeks. The application area was semi-occluded with 4-5 layers of gauze for 6 hours per dose, with 4 hours between doses. No treatment-related effects were observed in this study. The reported NOAEL was 450 mg/kg bw/day following exposure to the 30% azelaic acid pre-foam emulsion (US FDA 2015).

Genotoxicity

Based on the available data from in vitro and in vivo studies, the chemical is not expected to have genotoxic potential.

In an in vitro bacterial reverse mutation assay similar to OECD TG 471, azelaic acid up to 10 mg/plate was not mutagenic in strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) in the presence or absence of S9 metabolic activation (ECHA REACHa).

Negative results were reported for azelaic acid in an in vitro bacterial reverse mutation assay for mutagenicity when evaluated in two Ames tests (0.01–10 mg/plate; 0.1–5 mg/plate) with direct plate incorporation, in the presence and absence of metabolic activation (US FDA 2015).

A 20% azelaic acid cream was reported to give negative results in an Ames test, in vitro hypoxanthine-guanine phosphoribosyl transferase (HGRPT) assay and human lymphocyte test (with limited study details) (Fiume et al 2012).

In an in vitro bacterial reverse mutation assay conducted according to OECD TG 471, the lithium salt of azelaic acid was not mutagenic in strains of *S. typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) and *Escherichia coli* WP2 uvr A, in the presence or absence of S9 metabolic activation (ECHA REACHb).

In an HGPRT assay in V79 cells (Chinese hamster lung cells), azelaic acid (0, 0.19, 0.75, 1.32 and 1.88 mg/mL) was reported as negative for mutagenicity when evaluated in the presence and absence of metabolic activation (US FDA 2015).

Azelaic acid was not clastogenic in an in vitro human peripheral lymphocyte test in the presence (0, 120, 240, 480 and 960 µg/mL) and absence (0, 60, 120, 240 and 480 µg/mL) of metabolic activation (US FDA 2015).

In a mouse micronucleus assay, a single dose of azelaic acid (0, 500, 1000 and 2000 mg/kg bw) was administered orally (gavage) as a suspension to mice. Bone marrow was obtained

for analysis at 24 and 48 hours after administration. Azelaic acid was reported to not be clastogenic under the conditions of the assay (US FDA 2015).

In a dominant lethal assay, a single dose of azelaic acid (0, 500, 1000 and 2000 mg/kg bw) was administered orally (gavage) as a suspension to male mice. Following administration, males were mated with untreated female mice, for a mating period of 4 days. Females were replaced 11 times for a total of 48 days breeding period. In the high dose group, 4 of 50 males were deceased. No significant genotoxicity was reported to be observed in any mating interval, and no treatment related effects on fertility index, total implants, numbers of live or dead implants, or mortalities were reported (US FDA 2015).

Carcinogenicity

Based on the limited available data, the chemical is not expected to be carcinogenic.

A dermal carcinogenicity study in transgenic mice (Tg.AC assay) was conducted with 15% azelaic acid gel formulation. Topical doses of the formulation, at 0, 31.2 and 62.4 mg/day azelaic acid, were administered to mice for 26 weeks. A statistically significant increase in the incidence of papillomas was observed in males in the vehicle control and high dose groups. No effect was observed in females. However, there was no significant difference in the incidence of reported papillomas in the vehicle control and high dose males (US FDA 2015); therefore, it cannot be concluded that the effects are treatment related.

In a 2-year dermal mouse carcinogenicity study, azelaic acid pre-foam emulsion was administered twice daily to CD-1 mice at topical doses of 5%, 15% and 30% (500, 1500, and 3000 mg/kg bw/day azelaic acid). While no study method details are available, it is reported that no treatment related tumours were noted at concentrations up to 30% azelaic acid (Leo Pharma, 2020).

Reproductive and development toxicity

Based on the available information, the chemical is not expected to cause specific adverse effects on fertility or development. While embryotoxicity was noted in some animal studies, this was seen at doses that also resulted in maternal toxic effects.

In a reproductive and teratogenic study of azelaic acid in Wistar rats, the chemical was administered at 140 mg/kg bw/day in diet to 20 pregnant rats, while a control group of 10 pregnant rats was given untreated feed. Half of each group was necropsied on day 19 of gestation, with dosing of the remaining animals continued for a further 3 months. The day of gestation that dosing started was not specified. No gross or microscopic lesions were observed for the uteri, placentas, or ovaries. There were no reported difference in reproductive, teratogenic, or developmental effects between treated and control groups, nor were any differences in foetal weights of the live foetuses.

Similar results were reported to be seen in a study using groups of 20 gravid NZW rabbits fed 200 mg/kg bw/day of azelaic acid; 10 untreated gravid NZW rabbits were used as a negative control group (Fiume et al 2012). No other study details are available.

In a combined fertility and embryofoetal developmental study, azelaic acid was orally (gavage) administered at doses of 0, 50, 500 and 2500 mg/kg bw/day as a suspension to rats. While the number of animals per dose group is not specified, it is reported that the 500 and 2500 mg/kg bw/day dose groups contained 30 males each. Male rats were treated once daily for approximately 84 days (70 days prior to mating through to 14 days of mating).

Female rats were treated once daily for 48 or 71 days (14 days prior to mating through to day 20 of gestation, or through to day 21 post-partum). No effects on the fertility of the parental generation (P-generation), their offspring, or the general reproductive performance of the first generation (F1) pups, were reported. No teratogenicity was reported in the F1 or F2 generation pups. Mortalities (2 of 30 males) were observed at the highest dose. In the 500 and 2500 mg/kg bw/day groups, clinical signs of toxicity observed in the P0 generation males was stertorous (noisy) breathing in males, and lower body weight gain in both males and females. In the 2500 mg/kg bw/day group, the total intra-uterine deaths (post-implantation loss) were reported to be 3.7 times higher than the control group. Pup weights were also reported to be slightly lower (1–6%) on days 7, 14 and 21 at the highest dose, compared to the control group. The reported NOAEL for fertility and teratogenicity was 2500 mg/kg bw/day, while the NOAEL for embryotoxicity was 500 mg/kg bw/day (US FDA 2015).

In an embryofoetal developmental study, pregnant female rats were orally (gavage) administered azelaic acid at doses of 0, 50, 500 and 2500 mg/kg bw/day from gestation days 6-15. No teratogenicity was reported for any of dose groups. Clinical signs of toxicity were observed in the 500 and 2500 mg/kg bw/day dose groups (8 animals in each group), including retching reflex and stertorous breathing at the highest dose of 2500 mg/kg bw/day. While the mean number of early intra-uterine deaths (post-implantation loss) at the highest dose was reported to be 4 times higher compared with the control group, a lower maternal body weight gain (-17%) in comparison to the control group was reported at this dose. The reported NOAELs were 2500 mg/kg bw/day for teratogenicity, and 500 mg/kg bw/day for embryotoxicity. The NOAEL for maternal toxicity is considered to be 50 mg/kg bw/day in this study (US FDA 2015).

In a perinatal and postnatal developmental study, rats (25 animals/dose group) were orally (gavage) administered azelaic acid at doses of 0, 50, 500 and 2,500 mg/kg bw/day from gestation day 15 to day 21 post-partum. Mortalities were observed in the 500 and 2,500 mg/kg bw/day dose groups (1 and 2 animals, respectively). A significant decrease in body weight gain in dams from these two dose groups was also reported on day 20 post-coitum. At the highest dose, a significantly higher (+21%) mortality rate in the F1 animals was also reported. In addition to moderately lower body weights in F1 animals on day 90 post-partum, increased preimplantation loss in the F1 females and a slightly higher incidence of delayed ossification of single foetal bones in the F2 generation were observed compared to control animals. The reported NOAEL for developmental toxicity was 500 mg/kg bw/day, while the NOAEL for maternal toxicity was 50 mg/kg bw/day (US FDA 2015).

In embryofoetal developmental studies in rabbits and monkeys, azelaic acid was administered by oral gavage at doses of 0, 50, 150 and 500 mg/kg bw/day to pregnant female rabbits from gestation days 6–27, and pregnant female monkeys from gestation days 19–50.

In rabbits, a slight decrease in maternal body weight gain was observed in all dose groups compared to control animals. In the 150 and 500 mg/kg bw/day dose groups, the incidence of embryolethality was slightly higher (+4.1% and +4.5%, respectively) compared to control animals (statistical significance not reported). An increased incidence of incomplete or no ossification of the 5th sternebrae was observed in foetuses from all dose groups. No other effects were noted. The reported NOAEL for teratogenicity was 500 mg/kg bw/day, while for embryotoxicity was 50 mg/kg bw/day. The NOAEL for maternal toxicity is likely to be <50 mg/kg bw/day in this study (US FDA 2015).

In monkeys, a slight decrease in food consumption was observed in150 and 500 mg/kg bw/day dose groups compared to control animals. At 500 mg/kg bw/day, emesis was observed in addition to a higher incidence of spontaneous abortions compared to control

group animals. The reported NOAEL for teratogenicity was 500 mg/kg bw/day, while the NOAEL for embryotoxicity was 150 mg/kg bw/day. The NOAEL for maternal toxicity is likely to be <150 mg/kg bw/day in this study (US FDA 2015).

References

ASEAN (2020) Cosmetic Directive Annex II, Part 1 – List of substances which must not form part of the composition of cosmetic products, Version No. 2020-01, 27 October 2020.

Center for Disease Control (CDC) National Institute for Occupational Safety and Health (NIOSH) (1977) Health Hazard Evaluation Determination (Report No. 75-154-387), April 1977, Emery Industries, Cincinnati, Ohio.

Colón LE, Johnson LA and Gottschalk RW (2007) 'Cumulative irritation potential among metronidazole gel 1%, metronidazole gel 0.75%, and azelaic acid gel 15%', Cutis, 79(4):317-21.

European Commission Cosmetic Ingredient (COSING) Database. Accessed February 2021 at https://ec.europa.eu/growth/sectors/cosmetics/cosing_en

European Chemicals Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHa) Dossier. Azelaic Acid (CAS No. 123-99-9). Accessed January 2021 at https://echa.europa.eu/substance-information/-/substanceinfo/100.004.246

ECHA REACHb Dossier. Azelaic acid calcium salt (CAS No. 14488-58-5). Accessed May 2021 at https://echa.europa.eu/registration-dossier/-/registered-dossier/30153/7/7/2

Fiume MM, Heldreth B, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW and Andersen FA (2012) 'Final report of the Cosmetic Ingredient Review Expert Panel on the safety assessment of dicarboxylic acids, salts, and esters', Int J Toxicol, 31(4 Suppl):5S-76S.

Leo Pharma Inc. (2020) Finacea Full Prescribing Information, Accessed May 2021 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021470s015s016lbl.pdf

Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS) (2014) Aliphatic Acids SIDS Initial Assessment Report 6 September-30 October 2014. Accessed October 2020 at https://hpvchemicals.oecd.org/UI/handler.axd?id=47375d5b-e690-4977-a472-a8a89c25dc5c

Personal Care Products Council, Online INFOBASE, Accessed March 2021 at https://online.personalcarecouncil.org/jsp/Home.jsp

The Poisons Standard February 2021. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 32. Accessed March 2021 at https://www.legislation.gov.au/Series/F2020L01716

Safe Work Australia. Hazardous Chemical Information System (HCIS). Accessed May 2021 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

Sastri VR (2010) 'Engineering Thermoplastics', in *Plastics in Medical Devices*. Elsevier Inc.

Substances in Preparations in Nordic countries (SPIN) database. Accessed February 2021 at http://spin2000.net/

TGA (2021) Notice of final decisions to amend (or not amend) the current Poisons Standard, 22 April 2021. Accessed May 2021 at https://www.tga.gov.au/sites/default/files/notice-final-decisions-acms-32-accs-29-joint-acms-accs-26-november-2020-meetings.pdf

UNECE (2017). *Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Seventh Revised Edition*. United Nations Economic Commission for Europe (UNECE), Geneva, Switzerland. Accessed May 2021 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev07/07files_e0.html.

US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (2015) Pharmacology/Toxicology NDA Review and Evaluation, Application Number 207171, Accessed May 2021 at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207071Orig1s000PharmR.pdf