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

Retinal (Retinaldehyde)

Evaluation statement (EVA00186)

1 April 2026

Draft

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AICIS evaluation statement

Subject of the evaluation

Retinal (Retinaldehyde)

Chemical in this evaluation

CAS name	CAS number
Retinal	116-31-4

Reason for the evaluation

Evaluation is needed to provide hazard information.

Parameters of evaluation

The chemical is not listed on the Australian Inventory of Industrial Chemicals (the Inventory). Introduction into Australia as an industrial chemical has been reported to AICIS under the Reported and Exempted introduction categories. The chemical is structurally related to retinoic acid which is a known teratogen.

This evaluation of retinal is a human health hazard assessment for developmental toxicity only. The focus of the evaluation is to determine if the chemical has the human health hazard characteristic, developmental toxicity, for purpose of categorisation of industrial chemical introductions.

Summary of evaluation

Summary of introduction, use and end use

Based on information submitted to AICIS, the chemical is reported to be introduced in Australia for use in personal care products (cosmetic end use) at concentrations ranging from 0.015% to potentially up to 25%.

Human health

Summary of health hazards

Limited data are available for the chemical. Retinal is a synthetic and naturally occurring compound and member of a group of chemicals known as retinoids. Retinal is an intermediate in the metabolic conversion of retinol to retinoic acid.

The biological activity of retinoids, including retinal, is due to conversion to the biologically active metabolite, retinoic acid. The metabolic distance of a retinoid from retinoic acid

determines potency. As retinal is the immediate precursor to retinoic acid, it is expected to be more potent than retinol or retinol esters.

Therefore, data for developmental toxicity from metabolically related retinoids including retinyl palmitate, retinol and retinoic acid has been used to infer the developmental toxicity of the chemical.

Based on this data, retinal is expected to cause adverse effects on development of the unborn child. The weight of evidence indicate that this is primarily driven by transformation of these chemicals to the biologically active metabolite, retinoic acid.

The teratogenic effects of retinoic acid are well established. Similar teratogenic effects, specifically relating to abnormal development of the spine, deformities of limbs and craniofacial malformations, have been reported in animal studies and observations in humans following exposure to retinol and retinol esters. Available data indicate that the type and incidence of teratogenic effects is dependent on the timing at which exposure occurs, with the critical period in early stages of pregnancy.

Overall, the weight of evidence supports that the chemical is a presumed human developmental toxicant and as such classification is warranted.

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 hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Reproductive toxicity	Repr. 1B	H360D: May damage the unborn child

Proposed means for managing risk

As this evaluation is a hazard assessment only there are no proposed means for managing risks. However, as the evaluation has concluded that the chemical satisfies the criteria for classification according to the GHS, a recommendation to Safe Work Australia has been made.

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.

Conclusions

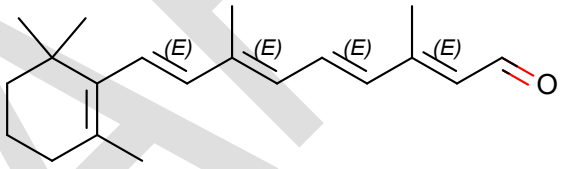
The chemical is presumed to produce adverse effects on the development of the offspring or effects on the offspring via lactation, as described in chapter 3.7 of the GHS, with the

chemical classified as Reproduction Category 1 (see **Hazard classifications relevant for worker health and safety**).

The Executive Director proposes to be satisfied that for the purpose of categorisation of industrial chemical introductions, the chemical has the human health hazard characteristic, developmental toxicity, in accordance with the Industrial Chemicals Categorisation Guidelines. This will mean that the chemical cannot be authorised for introduction into Australia for consumer end use, including in personal care products (cosmetics) under the exempted or reported introduction categories.

Supporting information

Chemical identity

CAS number	116-31-4
CAS name	Retinal
Molecular formula	$C_{20}H_{28}O$
Associated names	Retinaldehyde *all-trans*-Retinal Retinene 1
Molecular weight (g/mol)	284.44
SMILES (isomeric)	C(=C/C(=C/C=C/C(=C/C=O)/C)/C)\C=1C(C)(C)CCCC1C
Structural formula	

Relevant physical and chemical properties

Physical form	Crystalline solid
Melting point	63°C
Boiling point	314°C (predicted)
Vapour pressure	<0.01 Pa at 25°C (predicted)
Water solubility	<10.3 mg/L (predicted)
log Kow	6.61

Source of predicted data: US EPA CompTox Chemicals Dashboard v2.7.0

Health hazard information

Retinal is a synthetic and naturally occurring compound and member of a group of chemicals known as retinoids. Retinoids are essential for various physiological functions including vision, proliferation of epithelial tissues, immune functions, bone growth, and embryonic development.

Retinal is an intermediate in the metabolic conversion of retinol to retinoic acid (see **Toxicokinetics**).

The biological activity of retinoids, including retinal, is due to conversion to the biologically active metabolite, retinoic acid. The metabolic distance of a retinoid from retinoic acid determines potency. Retinal is the immediate precursor to retinoic acid; therefore, it is expected to be more potent than retinol or retinol esters (SCCS 2022, VKM 2012).

Therefore, it is considered appropriate to interpolate data for developmental toxicity from metabolically related retinoids including retinyl palmitate, retinol and retinoic acid.

Toxicokinetics

Toxicokinetic studies specific to retinal exposure are limited. Studies of both oral intake and dermal application have demonstrated that retinal is converted in vivo to the biologically active retinoic acid.

In a non-guideline study, pregnant Wistar rats (3 animals per group) received a single oral dose of retinal isomers at 100 mg/kg bw, on gestation day (GD) 13. Examination of blood plasma and maternal and foetal tissue taken at 1 hour and/or 2 hours after treatment showed an increase of isomers of retinoic acid with all-*trans* retinoic acid as the most abundant isomer (Sass et al. 1999).

In a non-guideline study, retinal at concentrations of 0.005, 0.01, 0.025, or 0.05% (equivalent to 25, 50, 125, or 250 µg) was topically applied daily for 9, 12 or 14 days, to the tail of C57BL/6 mice (3-6 animals per group). The animals were euthanised 20 hours after the last application. At the highest dose of retinal (250 µg), an increase of isomers of retinoic acid (all-*trans* retinoic acid and 13-*cis* retinoic acid) in tail skin tissue was detected after 14 days of treatment (Didierjean et al. 1996).

In a non-guideline study, the penetration into the epidermis (ex vivo human skin) of 4 topical retinoids, including retinal, in oil-in-water creams at 0.05% was investigated. Topical retinal was reported to penetrate well into the epidermis. A slight increase in levels of retinoic acid, retinol and retinol esters was detected in the epidermis (Antille et al. 2004).

Retinal is the metabolite formed by the oxidation of retinol. This is a reversible reaction, with reconversion of retinal to retinol catalysed by retinol dehydrogenase (RDH) or alcohol dehydrogenase (ADH). Retinal is further oxidized irreversibly to retinoic acid, primarily by retinaldehyde dehydrogenase (RALDH) (EFSA 2024; SCCS 2022; VKM 2012).

Reproductive and development toxicity

No data are available for the specific chemical. Based on available data for other metabolically relevant retinoids, the chemical is expected to cause adverse effects on development, warranting hazard classification.

The teratogenic potential of retinol and retinol esters (preformed Vitamin A) in both humans and animals has been widely reported and reviewed internationally. The weight of evidence from available studies indicate that this is primarily driven by transformation to the biologically active metabolite, retinoic acid.

Teratogenic effects, specifically relating to abnormal development of the spine, deformities of limbs and craniofacial malformations, have been reported in animal studies and observations in humans following exposure to retinol and retinol esters. A 2002 review by the European Commission Scientific Committee on Food (SCF) of available data on preformed vitamin A (retinol and retinyl esters), indicated that teratogenic effects (birth defects) similar to those observed following exposure to retinoic acid or other retinoids have been documented in cases of women who had ingested vitamin A during the early stages of pregnancy (SCF 2002). The SCF found that these cases confirm the link between excessive vitamin A intake and teratogenesis in humans, which it considered to be clearly documented in animals including rodents and non-human primates. It has also been indicated that the type and incidence of teratogenic effects depended on the timing at which exposure occurs, with the critical period in early stages of pregnancy. Subsequent international reviews have cited the 2002 SCF opinion, similarly, acknowledging the teratogenic potential of these chemicals in humans (COT 2022; EFSA 2006; EFSA 2015; EFSA 2024; EVM 2002; EVM 2003; SCCS 2016; VKM 2012). The data for retinol and retinol esters have been assessed concurrently (AICIS 2026). The draft evaluation for retinol and retinol esters concludes that these chemicals warrant GHS classification as Reproductive Category 1A H360D based on the evidence in humans. Key studies from the AICIS and international reviews relevant to the conclusions of that evaluation are summarised below.

Retinal is expected to be a more potent teratogen than retinol or retinol esters, as it is the immediate precursor to retinoic acid (see **Toxicokinetics** section).

The teratogenic effects of retinoic acid are well established. Retinoic acid binds to specific retinoic acid receptors (RARs), leading to upregulation of retinoid receptor genes which results in physiological effects. It has been reported that RARs show specific spatio-temporal patterns of expression, particularly during embryonic development. This suggests that retinoic acid signalling is involved in most, if not all, morphogenetic and patterning processes (COT 2022; Kurlandsky et al 1994; Theodosiou et al 2010; SCF 2002; VKM 2012).

Overall, the weight of evidence supports that the chemical is a presumed human developmental toxicant and as such classification of Reproductive toxicity 1B; May damage the unborn child is warranted. There are no human data for retinal to support classification in Category 1A.

Animal data

In a non-guideline study, a single oral dose of retinyl palmitate (CAS No. 79-81-2) was administered by gavage at 100, 300 or 1000 mg/kg bw to pregnant Riv:TOX rats (22–40 animals/group) on gestational day (GD) 10. All animals (including a control group) were also administered a dietary background level of the chemical at 5 mg/kg feed, over the preceding 6 weeks. Dams were euthanised on GD 11 or GD 21, and morphological assessment of conceptus was undertaken. A dose-dependent increase of the number of congenital malformations was reported, including the frequency of embryos at GD 11 with an open cranial neural tube (8.7% at 100 mg/kg bw, 23.8% at 300 mg/kg bw, 63.4% at 1000 mg/kg bw), compared with embryos from control group animals (1.5%). At GD 21, the high dose group showed an increase in late resorptions and a decrease in live foetuses per dam. Both the medium and the high dose groups had a high incidence of foetuses with malformations (71% and 97%, respectively), which included cleft palate, malformations of the

jaw, ears and eyes, and spina bifida; all commonly related to delayed neural tube closure (COT 2022; Piersma et al. 1996).

Similar effects were reported in a second experiment from the above study. Groups of pregnant Riv:TOX rats administered different dietary background levels of retinyl palmitate (1.5, 5, 15, or 50 mg/kg feed) were administered a single oral dose of the chemical on GD 10 at either 0 or 1000 mg/kg bw (14–17 animals/group). Dams were euthanised on GD 11 or GD 21, and morphological assessment of conceptus was undertaken. The increase in delayed neural tube closure, post-implantation loss and the incidence of malformations was similar across the groups treated with 1,000 mg/kg bw (COT 2022; Piersma et al. 1996). Maternal effects were not reported, and a lowest observed adverse effect level (LOAEL) or no observed adverse effect level (NOAEL) could not be established from either experiment in this study. It is noted that morphological assessment was only undertaken for live foetuses. Therefore, the occurrence of lethal malformations may be underrepresented in the reported data.

In a non-guideline study, pregnant Swiss-Webster mice (6–10 animals/group) were administered retinol (CAS No. 68-26-8) as a single oral dose at 0 (control groups) or 75 mg/kg bw (treatment groups) by gavage on either GD 7, 8, 9, 10 or 11. Dams were euthanised on GD 18 and morphological assessment of foetuses was undertaken. Teratogenic effects were observed in foetuses from treatment groups in the absence of maternal toxicity. The incidence and types of malformations appeared to relate to timing (GD) of treatment with the chemical. Treatment on GD 8 was reported to produce the highest incidence of embryonic deaths, whereas treatment on GD 10 was reported to not significantly increase the number of malformed foetuses compared with controls. Treatment on GD 7, 8 or 9 induced malformations of the palate, jaw, ears, eyes and head, while treatment on GD 11 induced forelimb development abnormalities. The incidence of unossified sternabrae was reported to be significantly increased in foetuses from dams exposed to the chemical on GD 9, compared with the control group (CIR 1987).

In a non-guideline study, pregnant Swiss albino mice (10-12 animals/group) were administered a single intraperitoneal (i.p.) injection of retinyl palmitate (CAS RN 79-81-2). It was administered at 15000 IU/kg (equivalent to 3.0 mg/kg bw), or 2 i.p. injections of the chemical in one day, 10 hours apart, at 10000 or 15000 IU/kg (equivalent to 2 doses of 3.0 mg/kg bw or 2 doses of 4.5 mg/kg bw, respectively, administered in one day). Doses were administered on GD 9, 10, 11 or 12, coinciding with the timing of limb morphogenesis in mouse embryos. Dams were euthanised on GD 18 and morphological assessment of conceptus was undertaken. A treatment-related and dose-dependent increase in the incidence of foetal limb malformations was reported: 9 (3.2%) incidences observed following one dose of 3.0 mg/kg bw/day, 49 (17.5%) at 2 doses of 3.0 m/kg bw and 65 (23.9%) at 2 doses of 4.5 m/kg bw. Limb malformations included micromelia (abnormally short limbs), absence of fingers or toes, and an increased cleft between metacarpal or metatarsal bones. A higher frequency of foetal limb malformations was observed in the GD 10–11 groups; the combined incidence across GD10 and 11 were 7 (5.2%) for the single 3.0 mg/kg bw dose group, 33 (23.9%) at 2 doses of 3.0 m/kg bw and 44 (40.0%) at 2 doses of 4.5 m/kg bw. An increase in the number of absorbed embryos was also observed in the GD 10–11 groups, comparative to the control group. Additional malformations were observed in foetuses from the highest maternal exposure group (2 i.p. injections of 4.5 mg/kg bw), these included mandibular hypoplasia (underdeveloped jaw), exencephaly (neural tube defect) and cleft palate (CIR 2013; Rezaei et al. 2009). It is noted that assessment of gross malformations was only undertaken for live foetuses.

In a non-guideline study in pregnant Cynomolgus monkeys (8–29 animals/group depending on dose), retinyl palmitate (CAS No. 79-81-2) was orally (nasogastric gavage) administered at 2.25, 6, 12 or 24 mg/kg bw/day (equivalent to 7500, 20000, 40000 and 80000 IU/kg bw/day) either once daily on GD 16–27, once daily on GD 16–25, then twice daily on GD 26 and 27. The period of exposure was based on an established sensitive period for induction of retinoid embryopathy in monkeys, which occurs during key stages of embryogenesis (gastrulation and neurulation) in this species (Gong et al., 2023; Hendrickx et al. 2000). The dosing regime was not expected to impact results. All animals, including controls, were additionally exposed to vitamin A via their daily food intake. The study was conducted across 2 laboratories with results combined. Foetal growth and development were monitored periodically using ultrasound. Maternal weights were recorded weekly throughout the study. Foetuses were surgically removed between GD 98 and GD 102 for examination.

Signs of maternal toxicity were reported in animals from the 2 highest dose groups (12 and 24 mg/kg bw/day), including erythema, skin rash, epistaxis, rhinorrhoea, swollen eyelids, gingivitis, lip lesions, and alopecia; these were reported as mild to severe signs of hypervitaminosis A. Maternal body weight gain was delayed in animals from the 2 highest dose groups compared to the control group. However, the mean maternal weights of the treated groups were comparable to the control group by the end of the observation period. At the highest dose, moderate to severe decreases in food intake were observed sporadically, which recovered after the cessation of treatment. No signs of maternal toxicity were observed in animals from the 2 lower dose groups (2.25 and 6 mg/kg bw/day).

Treatment-related and dose-dependent increases in foetal malformations and increase in abortions were reported to be statistically significant ($p \leq 0.0001$) (see **Table 1)**. Malformations were primarily observed in the craniofacial region. Malformations of the thymus and heart were observed in single foetuses.

Table 1: Developmental toxicity of retinyl palmitate in cynomolgus macaques (adapted from Hendrickx et al. 2000)

Dose Group (mg/kg bw/day)	No. of animals treated	No. of abortions	No. of malformations
0 (Control)	15	1 (7%)	0/14 (0%)
2.25	25	1 (4%)	0/24 (0%)
6	26	5 (19%)	1/22* (5%)
12	8	3 (38%)	2/6* (33%)
24	29	19 (66%)	5/11* (45%)

* Includes one nonviable foetus available for examination.

The NOAEL and LOAEL for developmental toxicity were reported to be 2.25 mg/kg bw/day (equivalent to 7500 IU/kg bw/day) and 6 mg/kg bw/day (equivalent to 20000 IU/kg bw/day), respectively, based on abortions and malformations (COT 2022; Hendrickx et al. 2000).

Observations in humans

A number of prospective cohort studies and case-control studies investigating teratogenic effects relating to exposure to preformed vitamin A are available. EFSA concluded that 3 of these studies had low risk of bias:

- A prospective case study (Rothman et al. 1995)
- Two case-control studies (Botto et al. 2001 and Johansen et al. 2008).

A prospective study assessed pregnancy outcome data relative to daily vitamin A intake of 22748 pregnant women. The study cohort was originally recruited between 1984 and 1987 to evaluate risk factors for neural-tube defects. Among these women, 339 had infants with birth defects, and 121 of those infants had abnormalities in structures derived from the cranial neural crest. For defects linked to cranial neural crest tissue, infants born to women who reported to consume more than 15000 IU/day of preformed vitamin A (4500 µg of retinol equivalents (RE) per day) from food and supplements had a prevalence rate 3.5 times higher than those whose mothers consumed 5000 IU/day (1500 µg RE/day) or less (95% confidence interval (CI)). When vitamin A intake from supplements alone was considered, infants of women who consumed more than 10000 IU/day (3000 µg RE/day) had a prevalence rate 4.8 times higher than those whose mothers consumed 5000 IU/day or less (95% CI). A smoothed regression curve suggested a threshold of about 10000 IU/day of supplemental vitamin A. The authors observed that a higher frequency of defects occurred among infants whose mothers reported to consume high levels of vitamin A before the seventh week of pregnancy, which covers the period of embryonic development in humans (EFSA 2024; Findlay et al. 2007; Rothman et al. 1995).

The case-control study by Botto et al. investigated the relationship between maternal intake of vitamin A and cardiac outflow tract defects (n=126). Retinol intakes from supplements >3000 µg RE/day were associated with a higher risk of transposition of great arteries (EFSA 2024). The Johansen et al. study investigated association between maternal intake of vitamin A from diet and supplements and risk of having a baby with an orofacial cleft (n=535). No increased risk of orofacial cleft or categories thereof were observed for high intakes of either retinol (>3398 µg RE/day) or total vitamin A (>3763 µg RE/day) (EFSA 2024).

In a multicentre prospective study, data for 311 infants born to mothers reported to be exposed to vitamin A at ≥10000 IU/day (≥3 mg RE/day) during the first 9 weeks of gestation were evaluated for the presence of major structural malformations. The median dose of vitamin A was 50000 IU/day (range, 10000-300000 IU/day). Among the infants born, 3 infants were reported to have a major malformation. No congenital malformations were reported among 120 infants exposed to more than 50000 IU/day of vitamin A. The authors concluded that while no evidence was found of an association between major structural malformations and intake of ≥3,000 µg RE/day, there were potential limitations in the study. This included the information source being mail or telephone interviews with mothers or their doctors (Mastroiacovo et al. 1999). This study was determined by EFSA to have a high risk of bias (EFSA 2024).

A range of case-controlled retrospective studies estimated the intake of vitamin A in mothers of malformed infants, comparative to control subjects. These studies differed in their classification of malformations, statistical power, and the quality of data on vitamin A consumption. Most studies found no association between moderate vitamin A intake (approximately 3000 µg RE) and foetal malformations. In addition, very few women reported consuming high levels of vitamin A, which substantially reduced the ability of these studies to detect any meaningful effect (Azais-Braesco and Pascal 2000; COT 2022).

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