Safety Assessment of Hydroxyacetophenone as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date (**June 25, 2021**) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.*

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ABBREVIATIONS

CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturing Association
GRAS	generally recognized as safe
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD	lethal dose
MMAD	mass median aerodynamic diameter
MeOH	methanol
MW	molecular weight
N/A	not applicable
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NR	not reported/none reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PDII	primary dermal irritation index
TG	test guideline
THF	tetrahydrofuran
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This assessment reviews the safety of Hydroxyacetophenone as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), this ingredient is reported to function in cosmetics as an antioxidant and skin-conditioning agent.[1]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[2] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

Hydroxyacetophenone (CAS No. 99-93-4) is the organic compound that conforms to the structure depicted in Figure 1.

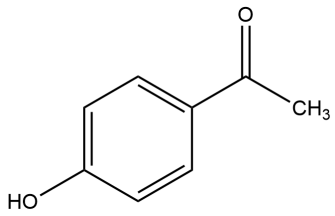

Figure 1 Hydroxyacetophenone

Chemical Properties

Hydroxyacetophenone has a molecular weight (MW) of 136.15 g/mol and an estimated log K_{ow} of 1.65.[2,3] The chemical properties of Hydroxyacetophenone are further outlined in Table 1.

Natural Occurrence

Hydroxyacetophenone, also known as piceol, and its glucoside, picein, have been found at concentrations of 0.4% - 1.1% and 1.8 - 2.2%, dry weight, respectively, in Norway spruce (*Picea abies*) needles.[4]

Method of Manufacture

No methods of manufacture were found in the published literature, and unpublished data were not provided.

Impurities

According to data in ECHA, the test substance Hydroxyacetophenone is reported at a purity of up to > 99%.[2] No further impurities data were found in the published literature, and unpublished data were not submitted.

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to the 2021 VCRP survey data, Hydroxyacetophenone is reported to be used in 531 formulations, of which 458 are leave-on products; there are165 reported uses in face and neck products and 139 reported uses in moisturizing products (Table 2).[5] Results from the 2020 concentration of use survey, conducted by the Council, indicate Hydroxyacetophenone has the highest maximum concentration of 5% in non-spray night products and in paste masks and mud packs, with the night product use representing the greatest maximum concentration for leave-on dermal exposure.[6]

This ingredient has been reported to be used in products that may come into contact with the eyes; for example, Hydroxyacetophenone is reported to be used at up to 0.23% in eye lotions and eye makeup removers. Hydroxyacetophenone is also reported to be used at up to 0.6% in formulations that could come in contact with mucous membranes, such as bath

soaps and detergents. Hydroxyacetophenone is reported to be used in 5 baby products; concentration of use data were not provided for this type of exposure.

Additionally, Hydroxyacetophenone is reported to be used in pump hair sprays and aerosol shaving creams (at up to 0.5%), as well as in face powder (concentration of use not reported), and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[7,8] Therefore, most droplets/ particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[9,10]. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[11-13]

Hydroxyacetophenone is not restricted from use in any way under the rules governing cosmetic products in the European Union.[14]

Non-Cosmetic

In 2011, the Joint Expert Committee on Food Additives (JECFA) mentioned Hydroxyacetophenone as a flavoring agent, and that it posed no safety concerns.[15] In Europe, Hydroxyacetophenone dietary exposure was estimated as 0.0002 µg/kg bw/d, while in Japan, Hydroxyacetophenone dietary exposure was estimated as 0.0059 µg/kg bw/d. Hydroxyacetophenone also has a Flavoring, Extract, and Manufacturing Association (FEMA) generally recognized as safe (GRAS) designation, under FEMA No. 4330.[16]

TOXICOKINETIC STUDIES

Toxicokinetics studies were not found in the published literature, and unpublished data were not submitted

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Hydroxyacetophenone (99.97% pure) was investigated following a single, occlusive application to New Zealand white rabbits.[2] Five male and 5 female New Zealand white rabbits (no controls used) were exposed to a single, undiluted dose of 2000 mg/kg Hydroxyacetophenone for 24 h, and were observed for mortality and clinical abnormalities for 14 d. No animals died during the observation period. All animals exhibited abnormal stools, ocular discharge, erythema, and edema at the test site; by day 13, all external abnormalities had resolved. Upon necropsy, no visible lesions were observed. The acute dermal LD_{50} in rabbits was > 2000 mg/kg bw.

Oral

The acute oral toxicity of Hydroxyacetophenone (99.97% pure) was determined in groups of 5 male and 5 female Sprague-Dawley rats using a single gavage exposure of 0, 1000, 2000, or 5000 mg/kg Hydroxyacetophenone, in corn oil.[2] The animals were observed for 14 d prior to necropsy. No animals in the control and 1000 mg/kg group died, while 3 male and 3 female rats from the 2000 mg/kg group and 4 male and all 5 female rats from the 5000 mg/kg group died; all animals died within 24 h of exposure. During the 14-d observation period, 8 of the 5000 mg/kg group animals, all 10 of the 2000 mg/kg group animals, and 8 of the 1000 mg/kg group animals exhibited one of the following: oral discharge, nasal discharge, ocular discharge, alopecia, abnormal respiration, tremors, abnormal stools, lethargy, and/or moribundity. Two of the control animals exhibited abnormal stools on day 0 while 1 animal exhibited a stained coat on day 3-9 of the observation period. Upon post-mortem examination, fluid was found in either the stomach, duodenum, jejunum, and/or ileum. The acute oral LD_{50} was determined to be 2240 mg/kg bw.

Short-Term Toxicity Studies

Oral

In a 28-d oral toxicity study, Hydroxyacetophenone (99.8% pure) was administered in propylene glycol, once daily by gavage, to groups of 5 male and 5 female Crl:WI(Han) rats at doses of 0, 40, 150, or 600 mg/kg bw, in accordance with Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 407.[2] No substance-related mortality or body weight gain occurred during the study period. No toxicologically significant changes were noted in hematology, clinical pathology, or organ weights, or upon gross and microscopic examination. The no-observed-adverse-effect-level (NOAEL) of Hydroxyacetophenone in rats was determined to be 600 mg/kg bw/d.

Inhalation

In an inhalation toxicity study, 10 male Sprague-Dawley rats and concurrent controls (number not specified) were exposed, whole body, 6 h/d and 5 d /wk for 4 wk, to a dust concentration of 42 mg/m^3 Hydroxyacetophenone (99.7% pure).[2] No mortality occurred during observation. The average mass median aerodynamic diameter (MMAD) was measured as 11 µm, with a standard deviation of 2.0 µm. More than 48% of the detected particles were found to be ≤ 10 µm. A statistically

significant decrease in albumin was observed after the first week of exposure, however these values returned to normal levels by the fourth week. The no-observed-adverse- effect-concentration (NOAEC) for inhalation toxicity in rats was determined to be 42 mg/m^3.

Subchronic Toxicity Studies

Oral

Groups of 20 male and 20 female Sprague-Dawley rats were dosed with 0, 5, 15, or 45 mg/kg Hydroxyacetophenone (100% pure), in corn oil, via gavage, in accordance with OECD TG 408, for 90 d.[2] One mid-dose female was sacrificed moribund on day 57, 1 control male was found dead on day 12, and mortality in 7 animals distributed across the groups was considered due to accidental deaths. Several (1-3) male animals from the control and most treated groups exhibited chromodacryorrhea or lacrimation, which were not considered treatment-related. No treatment-related effects were seen upon body weight, ophthalmoscopic examination, urinalysis data, and pathology. Mean food consumption was slightly elevated in males from the 45 mg/kg group during the last 4 wk, but these increases were generally not dose-related and therefore were not considered toxicologically significant. A month and a half into the study, a dose-related increase in reticulocytes was seen in males and females (groups not specified), which was not statistically significant. The NOAEL for Hydroxyacetophenone in rats was determined to be 45 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Groups of 5 male and 5 female Crl: WI (Han) rats were dosed with 0, 40, 150, or 600 mg/kg bw/d Hydroxyacetophenone, in propylene glycol, via gavage, in accordance with OECD TG 422.[2] Males were exposed for 30 d, including 2 wk prior to mating, up to the day before necropsy; females were exposed from 2 wk prior to mating up to at least 4 d of lactation, for a total of up to 46 d. Males were killed and examined shortly after mating, while females and pups were killed and examined after day 4 of lactation. One female in the 600 mg/kg group experienced total litter loss after delivery and was killed after 24 h; since other litters of the same group were comprised of live offspring, this finding was not considered toxicologically significant. No toxicologically significant changes or differences in fetal or pup body weights, viability, litter size, sex ratios, maturation, gross pathology, or developmental parameters were observed for any group. The NOAEL was determined to be 600 mg/kg bw/d for both males and females in the parental generation, as well as the F_1, generation.

GENOTOXICITY STUDIES

Details of the genotoxicity studies summarized below are described in Table 3.

Hydroxyacetophenone was not genotoxic in 3 separate bacterial reverse mutation assays, with concentrations ranging from 3 µmol/plate to 10,000 µg/plate.[2] In two gene mutation assays with L5178Y mouse lymphoma cells treated with concentrations of up to 1400 µg/ml Hydroxyacetophenone in the absence and presence of metabolic activation, diminished cell growth rate and increased mutant frequencies were observed.[2] Hydroxyacetophenone was not genotoxic at concentrations of up to 157 µg/ml in Chinese hamster ovary cell lines, with or without metabolic activation, in a sister chromatid exchange assay, or, in an in vitro cell transformation assay at concentrations of up to 1125 mg/ml using BALB/C-3T3 cell lines.[2] Groups of 5 male and 5 female ICR mice dosed with up to 450 mg/kg Hydroxyacetophenone in a micronucleus assay exhibited minimal clinical abnormalities, and 1 male from the 450 mg/kg group died on the third day following exposure; no significant increase in micronucleated polychromatic erythrocytes was noted in either sex at any dose.[2]

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

Four New Zealand white rabbits were treated with an occlusive, 6 cm^2, application of 0.5 g Hydroxyacetophenone, moistened with saline, to clipped skin, for 4 h.[17] Test sites were evaluated 72 h after patch removal, using the Draize scoring system. Slight dermal irritation was reported for 3 of the 4 test animals, including minimal erythema, without edema. (No further details provided).

In a similar irritation study, Hydroxyacetophenone (99.97% pure) was evaluated using 6 New Zealand white rabbits.[2] An occlusive application of 0.5 g solid test article, moistened with sterile water, was made neat to a shaved skin area of 1 in^2 for 4 h; an untreated skin site on the same animal was used as the control. The test sites were observed for up to 72 h. All control and treated sites were free of dermal irritation throughout the study period.

Groups of 6 New Zealand white rabbits were exposed to varying concentrations of Hydroxyacetophenone (99.87% pure).[2] Hydroxyacetophenone was diluted to 3%, 5%, 15%, and 30%, respectively, in 4 different vehicles: tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), methanol (MeOH), or *N,N*-dimethylformamide (DMF). The test articles (0.5 ml) were applied neat, and under occlusion, to a shaved area of 6 cm^2 for 4 h. An adjacent site on each treated animal was exposed to the respective vehicle (neat), and served as a vehicle control; an untreated site served as a negative control. After exposure, skin was wiped free of excess test material with an adsorbent pad and test sites were observed for up to 14 d. Test sites were evaluated for irritation using the Draize method, and all sites were scored 1, 24, 48, and 72 h after patch removal; test sites at which DMF and THF were used as the vehicle were observed at 7 d and up to 14 d, respectively. The maximum possible Draize score was 8.0. The primary dermal irritation index (PDII) was calculated using Draize scores recorded at 1, 24, 48, and 72 h after exposure. After 72 h, THF was shown to cause the most irritation, with a maximum mean Draize score of 7.5 (and average PDII of 6.5) at 0%; Hydroxyacetophenone in TMF produced maximum mean Draize scores of 7.5 at the 3% concentration, and 5.5 at the 30% concentration (with average PDIIs of 6.8 and 5.1, respectively). Lower scores were observed with the use of the other solvents, and scores were comparable across the concentrations with each vehicle; at the 30% concentration, Hydroxyacetophenone in DMSO had a maximum mean Draize score of 1.2 (and average PDII of 0.3), in MeOH had a maximum mean Draize score of 0.7 (and average PDII of 0.2), and in DMF had a maximum mean Draize score of 0.3 (and average PDII of 0.1). Recovery times were > 14 d for THF, 7 d for DMF, and 3 d for DMSO and MeOH. The test article did not significantly increase the dermal irritancy of any vehicle.

Sensitization

Animal

The sensitization potential of Hydroxyacetophenone was evaluated in a guinea pig maximization test.[2] Twenty male Hartley guinea pigs were first induced with an intradermal injection of 5% Hydroxyacetophenone (in propylene glycol, with and without Freund's complete adjuvant). Eight days later, the animals were induced for a second time with a topical application of 5% Hydroxyacetophenone in propylene glycol. Two wk after the second induction, a topical challenge application was made with 0.5 g of 75% Hydroxyacetophenone in petrolatum for 24 h. Dinitrochlorobenzene was used as a positive control (number of controls not specified). No sensitizing reactions were observed.

OCULAR IRRITATION STUDIES

Animal

The eyes of 4 healthy New Zealand white rabbits were treated with 0.1 g of undiluted Hydroxyacetophenone (99.97% pure) for 24 h.[2] The untreated eye of each animal served as the control, and both eyes were observed for up to 21 d after exposure. Potential for ocular irritancy was examined in the first animal leaving the treated eye unrinsed. In the remaining 3 animals, anesthetic was used prior to dosing, even for control eyes, and treated eyes were rinsed with approximately 120 ml of 0.9% saline, for 30 sec. In the animal with the unrinsed eye, corneal opacity, conjunctival redness, iridial irritation, chemosis, and discharge were noted, all of which resolved by 21 d. A maximum Draize score of 63, out of a maximum score of 110, was recorded for the unrinsed eye, 48 h after treatment; this score is categorized as a severe irritant. In the animals with rinsed treated eyes, milder conjunctival effects were seen, but resolved within 7 d; the mean Draize score calculated for the 3 animals with rinsed eyes was 22, categorizing the test article as a moderate irritant.

The ocular irritancy potential of Hydroxyacetophenone was investigated in the eyes of 4 healthy New Zealand white rabbits.[17] The right eyes of the animals were treated with 0.1 ml of finely ground Hydroxyacetophenone (duration not provided), and ocular lesions were scored approximately 24 h and 7 d following treatment by the Draize method. The treated eyes showed signs of moderate to severe discharge, moderate chemosis (swelling) and moderate to severe redness at the 24 h observation. Corneal opacity, severe ulceration, and mild iritis was observed in all 4 treated eyes. Three of the 4 treated eyes were free of corneal effects 7 d after treatment; moderate redness and chemosis persisted through day 7 for all 4 test animals. Hydroxyacetophenone was considered a severe eye irritant to rabbit eyes under these study conditions.

CLINICAL STUDIES

Case Reports

A 79-yr-old man experienced dermatitis for 7 mo on the right upper and lower eye lid with the use of prescription eyedrops and a facial cream containing Hydroxyacetophenone (concentration in cream not provided).[18] In spite of the eyedrop prescription being changed several times, these lesions did not subside. A 2-d patch test was conducted on the back, with allergens found in the Spanish baseline series, Chemotechnique fragrance series, all previously used eye drops, and the facial cream. All patch test results were negative on day 2 and 4, except for a ?+ reaction to the face cream. Results from a repeated open application test conducted on the upper arm with the facial cream showed erythema, infiltration, and papules. Further patch tests conducted on manufacturer-supplied, individual ingredients in the face cream, revealed positive reactions only to 0.6% aqueous Hydroxyacetophenone (+ on day 2 and ++ on day 4). Furthermore, eczematous lesions resolved within 5- d use of tacrolimus, and lesions did not develop after discontinued use of the face cream. Patch test results for Hydroxyacetophenone in 10 controls were all negative.

SUMMARY

The safety of Hydroxyacetophenone, as used in cosmetics, is reviewed in this safety assessment. According to the *Dictionary*, Hydroxyacetophenone is reported to function as an antioxidant and skin-conditioning agent.

In 2021 VCRP data, Hydroxyacetophenone has the highest reported use of 531 formulations, of which the two highest reported leave-on uses are in 165 face and neck products and 139 moisturizing products. Concentration of use survey data from a 2020 survey indicate that Hydroxyacetophenone has the highest reported maximum concentration of use of 5% in non-spray night products and paste masks and mud packs.

The acute dermal LD_{50} of Hydroxyacetophenone was > 2000 mg/kg bw in New Zealand white rabbits. Groups of 5 Sprague-Dawley rats were administered a single oral dose of up to 5000 mg/kg Hydroxyacetophenone, in corn oil, via gavage. Three male and 3 female rats from the 2000 mg/kg group, and 4 male and 5 female rats from the 5000 mg/kg group died within 24 h. During the 14-d observation period, 8 animals from the 5000 mg/kg group, all 10 in the 2000 mg/kg group, and 8 from the 1000 mg/kg group exhibited either oral discharge, nasal discharge, ocular discharge, alopecia, abnormal respiration, tremors, abnormal stools, lethargy, and/or moribundity; 2 control animals exhibited abnormal stools on day 0. The acute oral LD_{50} of Hydroxyacetophenone was determined to be 2240 mg/kg bw.

In a 28-d oral toxicity study, no toxicologically significant changes were noted in rats administered up to 600 mg/kg bw Hydroxyacetophenone; the NOAEL was determined to be 600 mg/kg bw/d. In an inhalation study, no mortality occurred in rats exposed, whole body, 6 h/d and 5 d/wk, for 4 wk, with 42 mg/m^3 Hydroxyacetophenone; a statistically significant decrease in albumin after the first week of exposure returned to normal levels by the fourth week. The NOAEC for inhalation toxicity in rats was, therefore, determined to be 42 mg/m^3.

Groups of 20 male and 20 female Sprague-Dawley rats were dosed with up to 45 mg/kg Hydroxyacetophenone, in corn oil, via gavage, for 90 d. One control male was found dead on day 12, and mortality in 7 animals across the dose groups (number not specified) was considered accidental deaths. Dose-related increases in the mean food consumption of males in the 45 mg/kg group and the reticulocytes in male and females (groups not specified) were not statistically significant. The NOAEL for Hydroxyacetophenone in rats was determined to be 45 mg/kg bw/d.

In an oral reproductive and developmental toxicity study, groups of 5 male and 5 female Crl: WI (Han) rats were dosed with 0, 40, 150, or 600 mg/kg bw/d Hydroxyacetophenone, in propylene glycol, via gavage, for up to 46 d. One dam in the 600 mg/kg group experienced total litter loss; however, because other litters of the same group were comprised of live offspring, this finding was not considered toxicologically significant. No toxicologically significant changes or differences in fetal developmental parameters were seen and the NOAEL was determined to be 600 mg/kg bw/d Hydroxyacetophenone for both males and females in the parental, as well as the filial, generation.

Hydroxyacetophenone was not genotoxic in 3 separate bacterial reverse mutation assays, at concentrations of up to 10,000 µg/plate, in the presence or absence of metabolic activation. In 2 gene mutation assays, L5178Y mouse lymphoma cells treated at concentrations of up to 1400 µg/ml Hydroxyacetophenone, in the presence or absence of metabolic activation, exhibited a diminished cell growth rate and increase in mutant frequencies. Hydroxyacetophenone was not genotoxic in a sister chromatid exchange assay, in which Chinese hamster ovary cell lines were treated with concentrations of up to 157 µg/ml, or in an in vitro cell transformation assay in which BALB/C-3T3 cell lines were treated with concentrations of up to 1125 mg/ml Hydroxyacetophenone. A significant increase of micronucleated polychromatic erythrocytes was not observed in ICR mice administered up to 450 mg/kg Hydroxyacetophenone.

Slight dermal irritation was reported for 3 of 4 New Zealand white rabbits treated with an occlusive, 6 cm^2 patch of 0.5 g Hydroxyacetophenone, moistened with saline, for 4 h. In a similar study, 0.5 g of Hydroxyacetophenone applied to rabbit skin in a 1 in^2, occlusive patch for 4 h, did not cause dermal irritation to control or treated sites. In a study comparing the dermal irritation potential of THF, DMSO, MeOH, or DMF, individually, and when 0.5 ml Hydroxyacetophenone was added to each, the test article did not increase the irritancy of any vehicle. In a maximization test, no sensitization occurred when male Hartley guinea pigs were induced twice with of 5% Hydroxyacetophenone, in propylene glycol, and challenged with a topical application 0.5 g of 75% Hydroxyacetophenone in petrolatum for 24 h,

New Zealand white rabbit eyes treated with 0.1 g of undiluted Hydroxyacetophenone, unrinsed, produced a Draize score of 63, categorized as a severe irritant, while eyes rinsed with 0.9% saline for 30 sec produced a Draize score of 22, categorized as a moderate irritant. In another study, New Zealand white rabbit eyes treated with 0.1 ml, finely ground Hydroxyacetophenone showed signs of moderate to severe discharge, moderate chemosis, and moderate to severe redness when scored 24 h following treatment. Corneal effects dissipated in 3 of the 4 treated eyes within 7 d after treatment; moderate redness and chemosis persisted through day 7 for all treated eyes.

A 79- yr-old man presented with dermatitis for 7 mo on the right upper and lower eye lid with the use of prescription eyedrops and a facial cream containing Hydroxyacetophenone (concentration in cream not provided). Positive patch-test reactions occurred for 0.6% aqueous Hydroxyacetophenone, which resolved with use of tacrolimus and discontinuation of cream use.

INFORMATION SOUGHT

The following information on Hydroxyacetophenone, as used in cosmetics, is being sought for use in the resulting safety assessment:

- Method of manufacture and impurities
- Dermal irritation and sensitization data at the maximum concentration of use

TABLES

Table 1, Chemical properties of Hydroxyacetophenone

Property	Value	Reference
Physical Form (@ 20 °C and 1013 hPa)	Solid	[2]
Molecular Weight (g/mol)	136.15	[3]
Specific Gravity (@ 20 ºC)	1.27	[2]
Vapor pressure (mmHg @ 20 ºC)	0.000015	[2]
Melting Point (°C @ 1013 hPa)	110	[2]
Water Solubility (g/l @ 22 ºC)	10	[2]
log K_{ow} (@ 25 °C)	1.35 (estimated)	[2]
Disassociation constants (pK_a @ 25 ºC)	8.05	[2]

Table 2. Frequency (2021) and concentration (2020) of use of Hydroxyacetophenone

	# of Uses[5]	Max Conc of Use (%)[6]
Totals*	**531**	**0.00009 - 5**
Duration of Use		
Leave-On	*458*	*0.02 - 5*
Rinse-Off	*73*	*0.000099 -5*
Diluted for (Bath) Use	*NR*	*0.25*
Exposure Type		
Eye Area	33	0.23
Incidental Ingestion	2	NR
Incidental Inhalation-Spray	6; 185[a]; 163[b]	0.3 – 0.5; 0.5[b]
Incidental Inhalation-Powder	1; 185[a]; 3[c]	0.075 – 0.3[c]
Dermal Contact	510	0.000099 - 5
Deodorant (underarm)	4[b]	NR
Hair - Non-Coloring	17	0.02 – 0.5
Hair-Coloring	NR	NR
Nail	2	NR
Mucous Membrane	15	0.000099 – 0.6
Baby Products	5	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders

NR – not reported

Table 3. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
Hydroxyacetophenone	3 µmol/plate, with and without metabolic activation	ethanol	*Salmonella typhimurium* strains TA 98, 100	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive control gave expected results.	[19]
Hydroxyacetophenone, 99.97% purity	Up to 5000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* TA 98, 100, 1535, 1537, 1538	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive control gave expected results.	[2]
Hydroxyacetophenone	1.0 -10,000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* strains TA 98, 100, 1535, 1537, 1538	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone, 99.97% purity	100- 1400 µg/ml without metabolic activation; 10-800 µg/ml with metabolic activation	DMSO	Mouse lymphoma L5178Y cells	Mammalian gene mutation assay	Clastogenic; Non-metabolically activated cultures treated with doses of 100-1400 µg/ml of the test article exhibited a growth rate of 103% to 34%, respectively, while activated cultures treated with concentrations of 10-800 µg/ml test article exhibited a growth rate of 76% to 13%, respectively. A dose-dependent response was not noted in the treated cultures. An increase in the frequency of small colonies in treated cultures, compared to control cultures, was consistent with damage to multiple loci on chromosome 11 in addition to loss of the TK locus. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	188-1250 µg/ml without metabolic activation; 31.5- 500 µg/ml	DMSO	Mouse lymphoma L5178Y cells	Mammalian gene mutation assay	Ambiguous genotoxicity; without metabolic activation, mutant cell frequencies were significantly increased only at very high toxicities (4.7 % relative growth). In the presence of metabolic activation, the test material was converted to more active form or forms. Treatments with 31.5 - 500 µg/ml test article when assayed produced mutant frequencies of 3.4- 5.6 fold, over a wide range of toxicities. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	4.7-157 µg/ml without metabolic activation or 47-1570 µg/ml with metabolic activation	DMSO	Chinese hamster ovary cell line	Sister chromatid exchange assay	Not genotoxic. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	62.5, 250, 400, 700, or 1125 mg/ml	NR	BALB/C-3T3 cells	In vitro cell transformation assay. BALB/C-3T3 cells were treated with chemical carcinogens, to test for cellular abnormalities in vitro and tumor growth when injected in animals.	Not genotoxic; No significant increase in the frequency of transformed foci was observed, corresponding to 19-114% cell survival for cultures treated with the lowest and highest concentration of the test substance. Appropriate negative and positive controls gave expected results.	[2]
			IN VIVO			
Hydroxyacetophenone, > 99% purity	0,113,225,450 mg/kg	Corn oil	Groups of 5 male and 5 female ICR mice	Micronucleus assay. Animals were given a single intraperitoneal dose; cyclophosphamide was used for the positive controls.	Not genotoxic; clinical abnormalities after dosing included lethargy, rough hair coat, and hunched posture. One male from the 450 mg/kg group died on the third day after treatment. No significant increase in micronucleated polychromatic erythrocytes was noted in either sex or for any dosage. Appropriate negative and positive controls gave expected results.	[2]

DMSO – dimethyl sulfoxide
NR – not reported

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