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Safety Assessment of Diacetone Alcohol as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Diacetone Alcohol as used in cosmetic formulations. This ingredient is reported to function as a fragrance ingredient and solvent. The Panel considered the available data and concluded that Diacetone Alcohol is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Keywords

Cosmetic Ingredient Review, Expert Panel for Cosmetic Ingredient Safety, Safety, Cosmetics, Diacetone Alcohol

Introduction

This is a safety assessment of Diacetone Alcohol as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), this ingredient is reported to function in cosmetics as a fragrance ingredient or solvent.[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This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated.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 Unpublished data are provided by the cosmetics industry, as well as by other interested parties.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 was found on the European Chemicals Agency (ECHA) database[2] or was available from the Organisation for Economic Cooperation and Development (OECD) Screening Information Dataset (SIDS) reports.[3] Please note that the ECHA website and OECD SIDS document provides summaries of information generated by industry, and when cited herein, it is those summary data that are incorporated into this safety assessment.

Chemistry

Definition and Structure

Diacetone Alcohol (CAS No. 123-42-2; molecular weight = 116.16 g/mol; log K_{ow} = 1.03) is a beta-hydroxy ketone formed by hydroxylation of 4-methylpentan-2-one at the 4-position.[4] According to the *Dictionary*, this ingredient is a ketone that conforms to the structure shown in Figure 1.

Chemical Properties

Diacetone Alcohol is a clear, colorless liquid with a faint, minty odor.[5] This ingredient is miscible in water, alcohol, ether, and other solvents.[6] A list of chemical properties for Diacetone Alcohol is provided in Table 1.

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Method of Manufacture

The following methods of manufacturing are general to the production of Diacetone Alcohol, and it is unknown whether they are used in the manufacture of Diacetone Alcohol for use in cosmetics.

Diacetone Alcohol is typically manufactured synthetically via the dimerization of acetone.[7,8] Diacetone Alcohol may be prepared by the action of alkali metal hydroxides (calcium hydroxide or barium hydroxide).[9] Acetone is first placed in a round-bottom flask with a Soxhlet extractor fitted with a reflux condenser. Two thimbles are placed in the extractor, each containing barium hydroxide and glass wool. The flask is then heated until the reaction is complete (approximately 95 to 120 h). The crude Diacetone Alcohol is then purified via distillation.

Impurities

According to an ECHA dossier, Diacetone Alcohol is reported to have a 99% to < 100% degree of purity.[2] In addition, acetone is reported to be a possible impurity of Diacetone Alcohol.

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 2021 VCRP survey data, Diacetone Alcohol is reported to be used in 107 nail formulations; uses were not reported in any other product category in the VCRP (Table 2).[10] However, the results of a concentration of use survey conducted by Council in 2019 indicate that Diacetone Alcohol is used in several different product categories. The highest maximum concentration of use reported is 9.2% in rinse-off shaving products (a "razor lube strip"); all other uses are at 0.84% or below. Diacetone Alcohol is used at up to 0.84% in nail polish and enamel formulations, and the highest concentration resulting in leave-on dermal exposure is 0.25% in "other" eye makeup preparations.[11] In many cases, reports of uses in certain categories were not reported in the VCRP, but concentration of use data were reported in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

Diacetone Alcohol is reported to be used in formulations near the eye (e.g., other eye makeup preparations) at

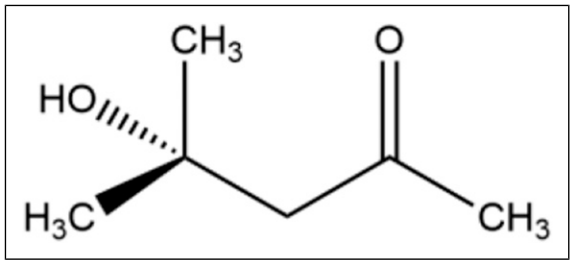

Figure 1. Diacetone Alcohol.

Table 1. Chemical Properties.

Property	Value	Reference
Physical form	Liquid	5
Color	Colorless	5
Odor	Faint, minty odor	5
Molecular weight (g/mol)	116.16	27
Density (g/ml @ 25°C)	0.94	26
Vapor pressure (mmHg @ 25°C)	0.97	28
Vapor density (mmHg)	4	29
Melting point (oC)	−43.89	26
Boiling point (oC)	167.78	5
Water solubility	Miscible	6
log K_{ow}	1.03	30

Table 2. Frequency (2021) and Concentration (2019) of Use of Diacetone Alcohol.[10,11]

	# of Uses	Conc of Use (%)
Totals[a]	107	0.00029-9.2
Duration of use		
Leave-on	106	0.00029-0.84
Rinse-off	1	0.00076-9.2
Diluted for (bath) use	NR	NR
Exposure type		
Eye area	NR	0.00099-0.25
Incidental ingestion	NR	NR
Incidental inhalation-spray	NR	NR
Incidental inhalation-powder	NR	0.0031[b]
Dermal contact	NR	0.00094-0.25; 9.2[c]
Deodorant (underarm)	NR	NR
Hair—non-coloring	NR	0.00029-0.0011
Hair—coloring	NR	0.014
Nail	107	0.1-0.84
Mucous membrane	NR	NR
Baby products	NR	0.00094-0.0011

[a]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.
[b]It is possible these products are powders, but it is not specified whether the reported uses are powders.
[c]"Razor lubricant strip."
NR—no reported use.

concentrations of up to 0.25%. It is also reported to be used in baby shampoos at up to 0.0011%.

Diacetone Alcohol is not restricted from use in any way under the rules governing cosmetic products in the European Union.[12]

Non-Cosmetic

Diacetone Alcohol is used as a solvent for cellulose acetate, nitrocellulose, celluloid, fats, oils, waxes, and resins.[6] It is also used in industrial coatings, household cleaners, inks, paints, paint removers, paint thinners, sealants, primers pesticides, antifreeze solutions, and hydraulic fluids.[13] Diacetone Alcohol is approved as an indirect food additive for the use of adhesives as a component (monomer) of articles intended for use in packaging, transporting, or holding food in accordance with the conditions prescribed in 21 CFR 175.105.[14]

Toxicokinetic Studies

Dermal Penetration

In Vitro. The in vitro dermal penetration rate of radiolabeled Diacetone Alcohol spiked with non-radiolabeled Diacetone Alcohol was studied in human cadaver skin taken from the abdominal region.[15] A minimum of six replicates represented by at least three donors were used. A standard in vitro diffusion cell model was used for this procedure. The test substance, in water, was applied to skin samples at a dose of 25 mg/cm^2 for either 10 min, 1 h, or 24 h. Total recovery (amount of test substance recovered in receptor solution), based on liquid scintillation count data for total radioactivity, was between 89.6 and 91.7% of the applied dose. Skin penetration (amount of test substance found in the skin) was 0.04, 0.15, and 5.71% of the dose after 10 min, 60 min, and 24 h, respectively.

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral. An evaluation of the plasma pharmacokinetic profile of Diacetone Alcohol was performed in 9 male Sprague–Dawley rats according to OECD Test Guideline (TG) 417.[2] Diacetone Alcohol (5.81 g) was weighed and mixed with 18.25 g corn oil, and administered to the animals via gavage. Blood samples were sampled from animals at 0.25, 0.5, 1, 2, 3, 6, 9, 12, and 24 h post-dosing. Diacetone Alcohol was quantifiable in the plasma via a gas chromatography-mass spectrometry method from 0.25 h to 24 h post-dosing. An initial plasma concentration peak at 4.40 mmol/l was reached 1 h post-dosing, but the maximum concentration was observed 6 h post-dosing, indicating a prolonged absorption phase. The terminal half-life was determined to be 2.3 h. The plasma levels of the potential metabolites, methyl isobutyl carbinol (MIBC) and methyl isobutyl ketone (MIBK), were below the lower limit of quantification at all time-points.

Toxicological Studies

Acute Toxicity Studies

Details regarding the acute toxicity studies summarized below are provided in Table 3.

The dermal LD_{50} in Wistar rats was >1875 mg/kg bw; this dose was applied for 24 h using an occlusive patch.[2] In rabbits, the dermal LD_{50} was reported to be 14.5 mL/kg in one study (occlusive 24-hour patch), and >13,630 mg/kg bw in another study (details not provided).[3] Several acute oral toxicity studies were performed with Diacetone Alcohol. LD_{50}s reported for mice and rabbits were 3950 and 4653 mg/kg bw, respectively. The lowest LD_{50} reported for rats was 2520 mg/kg bw.[16] An acute inhalation toxicity study was performed in Wistar rats exposed to aerosolized Diacetone Alcohol (7.6 mg/L) for 4 h.[2] The inhalation maximum tolerable concentration (LC_0) of Diacetone Alcohol was reported to be greater than 7.6 mg/L.

Short-Term Toxicity Studies

Oral. Groups of 10 albino rats (sex not specified) were given Diacetone Alcohol in drinking water for 30 days in concentrations resulting in doses of 0, 10, 40, or 130 mg/kg bw/d.[17] No deaths occurred throughout the study. In one rat dosed with 40 mg/kg bw/d, cloudy swelling and degeneration of renal tubular epithelium was noted. No adverse effects were reported in any rats at the 10 mg/kg bw/d dose level. No other details regarding this study were provided.

A combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was performed using SD(Crj:CD(SD)) SPF rats (10/sex/group) according to OECD TG 422.[2] Rats were treated with Diacetone Alcohol (purity: 99.8%) in water via gavage at doses of 30, 100, 300, or 1000 mg/kg bw/d. Males were treated for 44 days while females were treated for 41-45 days. Treated males and females were mated, and the F1 and parent generations were evaluated. Findings in parental animals included decreased locomotion and decreased response to stimulation in 300 and 1000 mg/kg bw/d males. Increases in platelet count, glutamic oxaloacetic transaminase, choline esterase, total protein, total cholesterol, total bilirubin, blood urea nitrogen, creatinine, and calcium, as well as a decrease in glucose at 1000 mg/kg bw/d, were observed in males and females. Increased kidney weights were noted at 300 and 1000 mg/kg bw/d in males, and increased liver and adrenal weights were noted in males treated with 1000 mg/kg bw/d. Histological evaluation of kidney tissues confirmed the presence of hyaline droplets in the proximal tubular epithelium in males dosed with 100 mg/kg bw/d or higher, and basophilic tubules in males dosed with 300 and 1000 mg/kg bw/d. Hepatocellular hypertrophy was

Table 3. Acute Toxicity Studies of Diacetone Alcohol.

Animals	No./ Group	Concentration/Dose/Protocol	LD50/Results	Reference
Dermal				
Wistar rats	6/sex	1875 mg/kg bw undiluted Diacetone Alcohol placed on skin under occlusive patch for 24 h; animals observed for 14-21 d post-dosing, in accordance with OECD TG 402	No reactions or clinical signs of toxicity observed; LD_0 was reported to be greater than 1875 mg/kg bw	2
Rabbits (strain not reported)	6/sex	Draize assay; undiluted Diacetone Alcohol was placed on the skin, under an occlusive patch, for 24 h; amount placed on skin not stated	LD_{50} was reported to be 14.5 mL/kg bw; there was no skin injury beyond erythema followed by shallow scaling	2
Rabbits (strain not reported)	NR	Up to 13,630 mg/kg bw; no other details reported	LD_{50} reported to be greater than 13,630 mg/kg bw	3
Oral				
Mice (strain not specified)	NR	NR	LD_{50} reported to be 3950 mg/kg bw	3
Wistar rats	6/sex/ group	1880, 2369, 3002, 3760, 5969 mg/kg bw administration via gavage; animals observed for 14 d after dosing, in accordance with OECD TG 401	Two out of the 12 animals administered 2369 mg/kg bw of the test substance died over a period of 14 d. All animals given 1880 mg/kg bw of the test substance survived the test period. Within a few hours of dosing, the rats were lethargic and displayed piloerection. One d after administration, animals were ataxic, and at high dose levels, comatose. The oral LD_{50} value of Diacetone Alcohol was determined to be 3002 mg/kg bw.	2
Wistar rats (male)	6/ex/ group	Animals were dosed via gavage; in accordance with OECD TG 401; specific dosing not stated	LD_{50} reported to be 4000 mg/kg bw; death was prompt and due to narcosis; survivors gained weight well	2
Rats (strain not specified)	NR	NR	LD_{50} reported to be 2520 mg/kg	16
Rats (strain not specified)	NR	NR	LD_{50} reported to be 4000 mg/kg bw	3
Rabbits (strain not specified)	NR	NR	LD_{50} reported to be 4653 mg/kg bw	3
Inhalation				
Wistar rats	5/sex	Rats exposed to test substance in an amount of 7.6 mg/L for 4 h; whole body exposure. Animals were observed for 14 d following exposure. Performed in accordance with OECD TG 402.	No animals died and no symptoms of toxicity were noted during the duration of the study or 14-day observation period. The inhalation maximum tolerable concentration (LC_0) of Diacetone Alcohol was reported to be greater than 7.6 mg/L.	2

NR = Not reported.

noted in the livers of male rats treated with 1000 mg/kg bw/d, and vacuolization of the cells of the zona fasciculata were noted in the adrenals of males treated with 300 and 1000 mg/kg bw/d. In females, a reduction of premating body weight gain, histopathological changes of the liver and adrenals, and an increase in liver weight was observed in high-dose females. Dilation of the distal tubules and fatty degeneration of the proximal tubule epithelium in the kidneys were noted in female rats dosed with 300 and 1000 mg/kg bw/d. The NOAEL for parental systemic toxicity was considered to be 100 mg/kg/d. Results regarding the reproductive effects evaluated in this study are presented in the Developmental and Reproductive Toxicity section of this report.

Inhalation. The potential inhalation toxicity of undiluted Diacetone Alcohol (purity: 99.44%) vapor was evaluated in

Wistar rats (12/sex/group) exposed to 0, 230, 1040, and 4500 mg/m^3 (analytical concentrations of 0, 233, 1041, and 4685 mg/m^3) of the test substance for 6 h/d, 5 d/wk, for 6 wk.[18] Rats were exposed in 1-m^3 chambers with a flow rate of approximately 0.45 m^3/min. No deaths occurred throughout the duration of the experiment. No clinical signs of toxicity were noted up until week 4 of exposure; however, during weeks 4 and 5, slight lethargy was noted in several of the animals exposed to the medium and high concentrations when they were examined 30 min after cessation of exposure. Body weights of females exposed to high concentrations were significantly lower than control animals at week 6. No significant differences were noted in any other group. Blood was taken from each rat 17 h after the last exposure session. Lactase dehydrogenase levels were significantly higher in females exposed to high concentrations compared to controls. In males, plasma protein levels were increased in the high-concentration group, plasma chloride levels were reduced in animals of the medium- and high-concentration groups, and plasma sodium levels were reduced in animals at all test concentrations. Examination of animals post-mortem showed male liver weights to be significantly higher than controls in the medium- and high-concentration groups, and male kidney weights were significantly higher than controls in the high-concentration group. The kidneys of all males, excluding one, exposed to the high concentration showed eosinophilic hyaline droplets in the proximal tubular cells. Other abnormalities included alveolar wall thickening and minor inflammatory infiltrates in the lungs, and similar infiltrates in the nasal cavities and trachea.

Subchronic Toxicity Studies

Oral. A subchronic toxicity study was performed according to OECD TG 408.[2] Sprague–Dawley rats were given Diacetone Alcohol in corn oil via gavage in doses of 0, 25, 150, or 600 mg/kg bw/d. Fifteen animals/sex were used in the 0 and 600 mg/kg bw/d test groups, and 10 animals/sex were used in the 25 and 150 mg/kg bw/d test groups. Animals were treated once daily for 13 weeks. On completion of the treatment period, animals in each group were sacrificed, with the exception of the recovery animals (5 animals/sex in the control and high-dose groups), which were kept for a 6-week treatment-free period. Non-adverse, slightly lower body weights were recorded from week 10 in males treated with the highest dose. When compared with controls, a slightly higher neutrophil count was noted in males treated with 600 mg/kg bw/d. In females, mean red blood cell count was statistically significantly decreased at 150 and 600 mg/kg bw/d when compared with controls, and was associated with lower hemoglobin and packed cell volume at the highest dose level. Lower total white blood cell and lymphocyte counts were also noted at the highest dose in females. Moderately higher cholesterol concentration was noted at 600 mg/kg bw/d in both males and females. In addition, in both sexes, administration of 600 mg/kg bw/d induced minimal to slight non-adverse centrilobular hepatocellular hypertrophy that correlated with increases in liver weights and with an increase in the incidence of macroscopically accentuated lobular pattern. In the kidneys of male rats, at the 25, 150, and 600 mg/kg bw/d dose levels, there were increased incidences and severity of tubular hyaline droplets, tubular basophilia, and granular casts, which correlated with increased kidney weights. Results regarding sperm analysis and estrous cycle monitoring can be found in the Developmental and Reproductive Toxicity Studies section of this report.

Developmental and Reproductive Toxicity Studies

A prenatal developmental toxicity study was performed in mated female Sprague–Dawley rats (24/group) according to OECD TG 414.[2] Diacetone Alcohol in corn oil was administered via gavage at doses of 100, 300, and 1000 mg/kg bw/d from day 6 to day 20 of gestation. A group of mated females received the vehicle only under the same experimental conditions and served as the control group. Animals were checked at least once daily for mortality and clinical signs. On day 21 post-coitum, animals were killed and submitted for a macroscopic post-mortem examination. All pregnant females had viable fetuses, and there were no unscheduled deaths. Excessive salivation and tremors were observed in dams treated with 1000 mg/kg bw/d. No effect on body weight, body weight change, or food consumption was observed at any dose level compared to controls. No test article–related effects were reported regarding uterus and carcass weights. A statistically significant increase was noted in mean relative liver and kidney weight values in dams treated with 1000 mg/kg bw/d when compared with controls. There were no effects on mean fetal body weight and sex ratio. In addition, there were no treatment-related effects at external examination and soft tissue examination of fetuses. Unossified or incomplete ossification of various parts of the skeleton was noted in all litters from mothers dosed with 1000 mg/kg bw/d. These findings were associated with presence of cartilage and were considered to be non-adverse effects of the test item treatment. A no-observed-adverse-effect level (NOAEL) for maternal parameters was considered to be 1000 mg/kg bw/d. The NOAEL for embryo–fetal development was considered to be 1000 mg/kg/d.

As described earlier in this report, a combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was performed using SD(Crj:CD(SD)) SPF rats (10/sex/group) according to OECD TG 422.[2] Rats were treated with Diacetone Alcohol in water via gavage at doses of 30, 100, 300, or 1000 mg/kg bw/d. Males were treated for 44 days while females were treated for 41-45 days (before and throughout pregnancy). Treated males and females were mated, and the F1 and parent generations were

evaluated. A decrease in fertilization rate, number of implantations, and implantation rate was observed at the 1000 mg/kg bw/d dose level. Reduced birth rate, delivery rate, and number of live pups at day 4 of lactation was observed in pups at the 1000 mg/kg bw/d dose level. In one 1000 mg/kg bw/d litter, no pups survived due to death or cannibalism. The NOAEL for reproductive function in males and females, as well as for development of offspring, was considered to be 300 mg/kg bw/d. Findings regarding other toxicity parameters evaluated in this study are provided in the Short-Term Toxicity Studies section of this report.

The possible reproductive effects of Diacetone Alcohol were evaluated in Sprague–Dawley rats, according to OECD TG 408.[2] As described previously in the Subchronic Toxicity Study section, rats were given Diacetone Alcohol in corn oil via gavage at doses of either 0, 25, 150, or 600 mg/kg bw/d. Fifteen animals/sex were used in the 0 and 600 mg/kg bw/d test groups, and 10 animals/sex were used in the 25 and 150 mg/kg bw/d test groups. On completion of the treatment period, animals in each group were sacrificed, with the exception of the recovery animals (5 animals/sex in the control and high-dose groups), which were kept for a 6-week treatment-free period. At the end of the treatment period, the number of cycles measured in female animals during a period of 21 days in the high-dose group was slightly lower than in the control group. At the end of the treatment-free period, this effect was no longer observed. There were no test article–related effects on mean epididymal sperm motility and morphology, mean testicular sperm head, and daily production rate. At the highest dose level, lower mean epididymal sperm counts were observed compared to controls; however, a relationship to the test article was considered to be unlikely in view of the low magnitude, the large standard deviations, the absence of microscopic finding in the testis and epididymis, and because individual values are comparable to what can typically be observed when Sprague–Dawley rats are used in laboratory conditions.

Genotoxicity

Details of the genotoxicity studies summarized below are provided in Table 4.

Diacetone Alcohol was not mutagenic in multiple Ames tests performed at up to 10,000 µg/plate, with and without metabolic activation.[2,19,20] Diacetone Alcohol was also evaluated in a yeast mitotic conversion assay (up to 5 mg/mL)

Table 4. Genotoxicity Studies of Diacetone Alcohol.

Test Substance	Concentration/ Dose	Vehicle	Test System	Procedure	Results	Reference
Diacetone Alcohol (purity: 99.8%)	0, 313, 625, 1250, 2500, and 5000 µg/plate	Water	*S. typhimurium* TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 uvr A	Ames test performed with and without metabolic activation	Non-mutagenic	2
Diacetone Alcohol (purity not stated)	100-10,000 µg/plate	Water	*S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538	Ames test performed with and without metabolic activation	Non-mutagenic	19
Diacetone Alcohol (purity not stated)	Up to 4000 µg/plate	Water	*S. typhimurium* strains TA1538, TA98, and TA100	Ames test performed with metabolic activation	Non-mutagenic	20
Diacetone Alcohol (purity: 99.70%)	0, 156.3, 312.5, 625, 1250, 2500, and 5000 µg/mL	Culture medium	Mouse lymphoma L5178Y (tk+/tk-) cells	Mouse lymphoma assay performed with and without metabolic activation	Non-mutagenic	2
Diacetone Alcohol (purity not stated)	100-10,000 µg/plate	NR	Mouse lymphoma L5178Y (tk+/tk-) cells	Mouse lymphoma assay performed with and without metabolic activation	Non-mutagenic	21
Diacetone Alcohol (purity not stated)	Up to 5 mg/mL	Water	*Sacc. cerevisiae* JD1	Yeast mitotic assay performed with metabolic activation	Non-mutagenic	20
Diacetone Alcohol (purity not stated)	Up to 4000 µg/ml	Water	Rat liver (RL_4) cells	Chromosome assay performed without metabolic activation	A small increase in chromatid damage was observed within the concentration range of 2000-4000 µg/ml.	20

and a chromosome assay (up to 4000 µg/ml).[2,20] Metabolic activation was used in the yeast mitotic assay. The test substance did not induce reverse gene mutation in bacteria or mitotic gene conversion in yeast; however, in the rat liver chromosome assay, a small increase in chromatid damage was observed within the concentration range of 2000-4000 µg/ml. No chromosomal damage was observed in the chromosomal aberration assay. Mouse lymphoma assays performed on Diacetone Alcohol at up to 10 000 µg/plate with and without metabolic activation yielded negative results.[2,21]

Carcinogenicity Studies

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

Dermal Irritation and Sensitization

Irritation

Animal. A dermal irritation assay was performed according to OECD TG 404.[2] Undiluted Diacetone Alcohol (0.5 mL) was applied to the shaved skin of New Zealand white rabbits (3/sex) under an occlusive patch. Two test sites were evaluated per animal, one intact and one abraded. Patches remained on the skin for 24 h. The intact and abraded test sites were examined and scored for erythema and edema at 24 h, 72 h, and 7 d after application. Very slight, transient erythema was observed in 3 animals with abraded skin, which was fully reversible by day 3 in all animals. No irritation was observed in animals with intact skin.

Irritation was also evaluated by brushing the inside of the right ear of rabbits with Diacetone Alcohol, once per day, for 10 successive days.[22] No skin irritation was reported. Similarly, no irritation was observed when guinea pigs were exposed to Diacetone Alcohol on the back, once per day, for 10 consecutive days. Details regarding dosing and number/strain of animals were not reported in either study.

Human. No itching or irritation was reported when a coin-sized amount of Diacetone Alcohol was placed on the back of the hands of human volunteers.[22] The substance evaporated, and the spots on the skin remained healthy thereafter. No other details regarding this study were provided.

Sensitization

Animal. A guinea pig maximization test was performed according to OECD TG 406.[2,23] Thirty Dunkin–Hartley guinea pigs were allocated into two groups: a control group (5 animals/sex) and a treated group (10 animals/sex). On day 1, intradermal injections of an adjuvant mixed with the test substance (25% Diacetone Alcohol (purity: 99.72%) in sterile isotonic saline solution) or the vehicle were performed in the dorsal region between the shoulders. On day 7, sodium lauryl sulfate was topically applied to the previously injected site to induce local irritation. On day 8, the same test site was treated with undiluted Diacetone Alcohol or vehicle, and was covered by an occlusive dressing for 48 h. After a 12-day non-treatment period, all animals were challenged with a 24-hour occlusive patch of undiluted Diacetone Alcohol that was applied to the right flank. The left flank served as a control and received the vehicle only. Skin reactions were evaluated 24 and 48 h after application. No cutaneous reactions were observed after the challenge application. The test substance was considered to be non-sensitizing.

Ocular Irritation Studies

Animal

Undiluted Diacetone Alcohol (0.1 mL) was placed in the eyes of 3 rabbits (strain not stated).[2] Animals were observed 1 h and 1, 2, 3, 4, 7, and 14 d post-treatment, and irritation was scored via a Draize scale (maximum score of 4). Slight to moderate conjunctival irritation, slight iritis, and slight to mild corneal opacity was observed. All effects were fully reversible. The mean individual scores over 24, 48, and 72 h were 1.3, 1.7, and 1.7 for chemosis; 1.7, 2.3, and 2.0 for conjunctival redness; 0.3, 1.0, and 0.7 for iritis; and 1.3, 1.0, and 1.7 for corneal opacity. It was concluded that Diacetone Alcohol is irritating to the eyes of rabbits.

In a different study, albino rabbit eyes were treated with 0.005 mL of undiluted Diacetone Alcohol, with the lids retracted.[24] The number of test animals were not stated. After approximately 1 min, the lids were released. Eighteen to 24 h later, the eyes were examined in strong diffuse daylight, then stained with fluorescein to assess injury on a scale of 1-10. Diacetone Alcohol was reported to cause grade 5 injury (on a scale of 1-10).

Human

Ocular irritation was apparent in 12 male and 12 female subjects exposed to vaporized Diacetone Alcohol at a concentration of 100 ppm for 15 min.[25] No other details regarding this study were provided.

Clinical Studies

Inhalation Exposure

Potential respiratory irritation from Diacetone Alcohol was evaluated in humans (12/sex).[25] Subjects were exposed to vaporized Diacetone Alcohol in a concentration of 100 ppm for 15 min. The majority of the subjects found the odor unpleasant at 100 ppm, complained of an unpleasant taste, and irritation to nose and throat. Although the majority of the subjects indicated that they could work an 8-hour day in 100 ppm, 50 ppm appeared to be a more reliable limit. It was

concluded that Diacetone Alcohol is irritating to the respiratory tract.

Occupational Exposure Limits

The National Institute for Occupational Safety and Health (NIOSH) established a recommended inhalation exposure limit of 50 ppm for Diacetone Alcohol over a 10-hour work-day.[5] Similarly, the permissible exposure level for Diacetone Alcohol exposure over an 8-hour work-day was determined to be 50 ppm, according to Occupational Safety and Health Administration (OSHA).[26]

Summary

This assessment addresses the safety of Diacetone Alcohol as used in cosmetics. According to the *Dictionary*, this ingredient is reported to function as a fragrance ingredient and solvent in cosmetic formulations.

According to 2021 VCRP data, Diacetone Alcohol is reported to be used in 107 nail formulations. Uses were not reported in any other product category; however, according to the concentration of use survey conducted by Council in 2019, concentrations have been reported for nail formulations, as well as other categories. The highest concentration of use reported for Diacetone Alcohol in leave-on products is 0.84% in nail polish and enamel, and the highest concentration resulting in leave-on dermal exposure is 0.25% in "other" eye makeup preparations.

The in vitro dermal penetration rate of Diacetone Alcohol (25 mg/cm^2) was studied in human cadaver skin. Skin penetration (amount of test substance found in the skin) was 0.04, 0.15, and 5.71% of the dose after 10 min, 60 min, and 24 h, respectively. The plasma pharmacokinetic profile was studied in nine male Sprague–Dawley rats given Diacetone Alcohol (5.81 g) mixed with corn oil (18.25 g) via gavage. An initial plasma concentration peak at 4.40 mmol/l was reached 1 h post-dosing, but the maximum concentration was observed 6 h after post-dosing, indicating a prolonged absorption phase.

The dermal LD_{50} in Wistar rats was >1875 mg/kg bw; this dose was applied for 24 h using an occlusive patch. In rabbits, the dermal LD_{50} was reported to be 14.5 mL/kg in one study (occlusive 24-hour patch), and >13,630 mg/kg bw in another study (details not provided). Several acute oral toxicity studies were performed with Diacetone Alcohol. The lowest LD_{50}s reported for mice, rats, and rabbits were 3950, 2520, and 4653 mg/kg bw, respectively. An acute inhalation toxicity study was performed in Wistar rats exposed to aerosolized Diacetone Alcohol (7.6 mg/L) for 4 h.[2] The inhalation maximum tolerable concentration (LC_0) of Diacetone Alcohol was reported to be greater than 7.6 mg/L.

In a 30-day oral toxicity study, 10 albino rats were given Diacetone Alcohol in drinking water at doses of 0, 10, 40, or 130 mg/kg bw/d. No deaths occurred throughout the study. In one rat dosed with 40 mg/kg bw/d, cloudy swelling and degeneration of renal tubular epithelium was noted. No adverse effects were reported in any rats at the 10 mg/kg bw/d dose level. In a combined repeated dose toxicity study with a reproduction/developmental toxicity screening test performed in SD(Crj:CD(SD)) SPF rats, groups of 10 rats/sex were treated with Diacetone Alcohol in water via gavage at doses of 30, 100, 300, or 1000 mg/kg bw/d. Males were treated for 44 days while females were treated for 41-45 days. Treated males and females were mated, and the F1 and parent generations were evaluated. Signs of toxicity, such as increases in organ weights and abnormalities in kidney tissues, were observed in animals given high doses of the test substance. In a 13-week oral toxicity study, Sprague–Dawley rats were given Diacetone Alcohol in corn oil via gavage once daily. Fifteen animals/sex were given 0 or 600 mg/kg bw/d, and 10 animals/sex were given 25 or 150 mg/kg bw/d. In females, mean red blood cell counts were statistically significantly decreased at 150 and 600 mg/kg bw/d when compared with controls. Lower total white blood cell and lymphocyte counts were also noted at the highest dose in females. In the kidneys of male rats in the 25, 150, and 600 mg/kg bw/d dose levels, there were increased incidences and severity of tubular hyaline droplets, tubular basophilia, and granular casts, which correlated with increased kidney weights.

The potential inhalation toxicity of undiluted Diacetone Alcohol was evaluated in Wistar rats (12/sex/group). Rats were exposed to up to 4500 mg/m^3 of the test substance for 6 h/d, 5 d/wk, for 6 weeks. No clinical signs of toxicity were noted during the first 4 weeks of exposure. Decreases in body weight and abnormalities in the kidneys were observed in animals treated with a high concentration of the test substance.

A prenatal developmental toxicity study was performed in mated female Sprague–Dawley rats (24/group). Diacetone Alcohol in corn oil was given to the test animals at doses of up to 1000 mg/kg/d on days 6-20 post-coitum. No toxic effects were noted in offspring. The NOAEL for maternal parameters was considered to be 1000 mg/kg/d, and the NOAEL for embryo–fetal development was considered to be 1000 mg/kg/d. A different study was performed in order to evaluate the reproductive/developmental toxicity of Diacetone Alcohol (up to 1000 mg/kg bw/d) in SD(Crj:CD(SD)) SPF rats (10/sex/group). Males were treated for 44 days while females were treated for 41-45 days (before and throughout pregnancy). Treated males and females were mated, and the F1 and parent generations were evaluated. The NOAEL for parental systemic toxicity was considered to be 100 mg/kg/d and the NOAEL for reproductive function in males and females, as well as for development of offspring, was considered to be 300 mg/kg bw/d. The possible reproductive effects of Diacetone Alcohol (up to 600 mg/kg/d) were evaluated in Sprague–Dawley rats via a sperm analysis and monitoring of estrous cycles. At the end of the treatment period, the number of cycles measured in female animals during a period of 21 days in the high-dose group was slightly lower than in the control group. At the highest dose level, lower mean

epididymal sperm counts were observed compared to controls; however, a relationship with the test item was considered to be unlikely in view of the low magnitude, the large standard deviations, the absence of microscopic finding in the testis and epididymis, and because individual values are comparable to what can be observed in Sprague–Dawley rat laboratory conditions.

Diacetone Alcohol was negative in multiple Ames tests performed at up to 10,000 µg/plate, with and without metabolic activation. Diacetone Alcohol was also evaluated in a yeast mitotic conversion assay (up to 5 mg/mL), and a chromosome assays (up to 4000 µg/ml). Metabolic activation was used in yeast mitotic assay, but was not used in the chromosome assay. The test substance did not induce reverse gene mutation in bacteria or mitotic gene conversion in yeast; however, in the rat liver chromosome assay, a small increase in chromatid damage was observed within the concentration range of 2000-4000 µg/ml. A mouse lymphoma assay performed on Diacetone Alcohol at up to 10 000 µg/plate with and without metabolic activation yielded negative results.

The irritation potential of undiluted Diacetone Alcohol to intact and abraded skin was evaluated in New Zealand white rabbits (3/sex). After a 24-hour application under an occlusive patch, slight, transient erythema was observed in three animals with abraded skin, and no irritation was observed in animals with intact skin. In a different study, Diacetone Alcohol was brushed on the ears of rabbits, once per day, for 10 days. No irritation was observed. Similarly, no irritation was reported when guinea pigs were exposed to Diacetone Alcohol on the back, once per day, for 10 days. In a human study, no itching or irritation was reported when a coin-sized amount of Diacetone Alcohol was placed on the back of the hands of volunteers.

A guinea pig maximization test was performed using Dunkin–Hartley guinea pigs (10/sex). Undiluted Diacetone Alcohol was used during the epicutaneous induction and challenge exposure. No cutaneous reactions attributable to the sensitization potential of Diacetone Alcohol were observed in the test animals.

Undiluted Diacetone Alcohol (0.1 mL) was placed in the eyes of 3 rabbits (strain not stated) to observe potential eye irritation. Slight to moderate conjunctival irritation, slight iritis, and slight to mild corneal opacity was observed. All effects were fully reversible. In a different study, albino rabbit eyes were treated with 0.005 mL of undiluted Diacetone Alcohol. On a scale of 1-10, Diacetone Alcohol was reported to cause grade 5 injury. Ocular irritation was apparent in 12 male and twelve females exposed to vaporized Diacetone Alcohol in a concentration of 100 ppm for 15 min.

Potential respiratory irritation from Diacetone Alcohol was evaluated in humans (12/sex). Subjects were exposed to vaporized Diacetone Alcohol in a concentration of 100 ppm for 15 min. The majority of the subjects found the odor unpleasant at 100 ppm, complained of an unpleasant taste, and irritation to nose and throat. It was concluded that Diacetone Alcohol is irritating to the respiratory tract.

NIOSH has established a recommended inhalation exposure limit of 50 ppm for Diacetone Alcohol over a 10-hour work-day. Similarly, OSHA established a permissible exposure level of 50 ppm over an 8-hour work-day.

Discussion

Diacetone Alcohol is a beta-hydroxy ketone that is reported to function as a fragrance ingredient and solvent in cosmetics. According to 2021 VCRP data, this ingredient is only used in nail product formulations; however, 2019 concentration of use data indicate in addition to nail product formulations, Diacetone Alcohol is also used in other cosmetic formulation types (e.g., eye makeup, shaving preparations, and skin cleansing). The Panel found that the systemic toxicity data and the dermal irritation and sensitization data in this report were sufficient, and determined Diacetone Alcohol is safe in cosmetics in the present practices of use and concentration. The need for carcinogenicity data was mitigated by multiple negative genotoxicity assays. Safety of this ingredient was further supported by low concentrations of use in leave-on products. Also, because Diacetone Alcohol is used at low concentrations of use, expected amounts of exposure to possible impurities would be extremely low, mitigating the need for further Diacetone Alcohol impurities data.

The Panel discussed the issue of potential incidental inhalation exposure from powders. The Council survey results indicate that Diacetone Alcohol is used in face, neck, and night products, which may be formulated as powders, at up to 0.0031%. Furthermore, particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings. In addition, the Panel noted the available acute and short-term inhalation studies, and determined that inhalation exposure to Diacetone Alcohol via cosmetic use would not be of concern.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that Diacetone Alcohol is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 555 13th St., NW, Suite 300W, Washington, DC 20004. cirinfo@cir-safety.org

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