Safety Assessment of Amyl Acetate and Isoamyl Acetate as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	May 23, 2022
Panel Meeting Date:	June 16-17, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Senior Scientific Analyst/Writer, CIR
Date: May 23, 2022
Subject: Re-Review of the Safety Assessment of Amyl Acetate and Isoamyl Acetate

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of Amyl Acetate and Isoamyl Acetate in 1988, with the conclusion that these ingredients are safe in the present practices of use and concentration, as described in the safety assessment. The original report is included for your use (identified as *originalreport_AmylAcetate_062022* in the pdf).

Because it has been at least 15 years since the previous safety assessment was published, in accord with Cosmetic Ingredient Review (CIR) Procedures, the Panel should consider whether the safety assessment of Amyl Acetate and Isoamyl Acetate should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1982 forward. An historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed herein (*newdata_AmylAcetate_062022)*.

New studies that were found as a result of the literature search include subchronic and developmental inhalation toxicity assays using Amyl Acetate, all yielding high NOAELs. Also found were genotoxicity assays using Isoamyl Acetate, all of which resulted in negative results. Two previous RIFM safety assessments reviewing Amyl Acetate and Isoamyl Acetate were also found. The Expert Panel for Fragrance Safety concluded that these ingredients are safe under the limits described in the safety assessments.

Also included for your review is a table of current and historical use data (*usetable_AmylAcetate_062022).* The frequency and concentration of use for Amyl Acetate has decreased from 18 to 4 uses, and from < 10% to ≤ 0.09%, respectively. In 1988, Isoamyl Acetate was not reported to be in use; however, according to 2022 FDA VCRP data, this ingredient in now used in 1 formulation (up to 0.22%).

If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a Draft Amended Report will be presented at an upcoming meeting.

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Re-Review - Amyl Acetate and Isoamyl Acetate - History and New Data

(Priya Cherian – June 2022 meeting)

Ingredients (2)	Citation	Conclusion	Use - New Data	Use - Historical Data	Notes
Amyl Acetate **Isoamyl Acetate**	JACT 7(6):703-19, 1988	safe as used	Amyl Acetate frequency of use (2022): 4 uses concentration of use (2021): ≤ 0.09% (rinse-off); ≤ 0.05% (leave-on) Isoamyl Acetate frequency of use (2022): 1 use concentration of use (2021): ≤ 0.22% (rinse-off); ≤ 0.075% leave-on	Amyl Acetate frequency of use (1987): 18 uses concentration of use (1987): ≤ 10% (leave-on) Isoamyl Acetate frequency of use (1987): NR concentration of use (1987): NR .	frequency and concentration of use decreased ; in 1987, uses were only reported for nail products frequency and concentration of use now reported for this ingredient

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Gill MW, Tyler TR, Beyrouty PC. Subchronic inhalation neurotoxicity study of amyl acetate in rats. J Appl Toxicol. 2000 Nov-Dec;20(6):463-9.	Subchronic Inhalation Toxicity	-Sprague-Dawley rats (10-15/sex/group) treated with Amyl Acetate vapor (full-body exposure; 0, 300, 600, or 1200 ppm) -6 h exposures; 13 wk total -No overt clinical signs of toxicity observed -NOAEL of greater than 1200 ppm established	Amyl acetate resulted in toxic effects at concentrations of 5200 ppm in rats, and as low as 5000 ppm in cats – as stated in previous report
SIDS Initial Assessment Report for 22nd SIAM UNEP Publications (2006) Retrieved from: https://hpvchemicals-oecd-org.lp.hscl.ufl.edu/ui/handler.axd?id=8785D1F3-5241-47AE-85C3-1505F707F9AF	Subchronic Inhalation Toxicity	-Sprague-Dawley rats (20/sex) treated with primary Amyl Acetate (65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate); 0, 100, 400, or 500 ppm -whole-body inhalation; 14 wk -no signs of toxicity -NOAEL of 500 ppm	Same as above
SIDS Initial Assessment Report for 22nd SIAM UNEP Publications (2006) Retrieved from: https://hpvchemicals-oecd-org.lp.hscl.ufl.edu/ui/handler.axd?id=8785D1F3-5241-47AE-85C3-1505F707F9AF	Developmental Toxicity - Inhalation	-Pregnant female Fischer 344 rats (25 rats/group) exposed to primary Amyl Acetate (65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate); 0, 500, 1000, 1500 ppm -6 h exposures; GD 6-15 -NOAEL for maternal toxicity determined to be 500 ppm -NOAEL for developmental toxicity considered to be 500 ppm	No developmental/reproductive toxicity data were available in the last report
SIDS Initial Assessment Report for 22nd SIAM UNEP Publications (2006) Retrieved from: https://hpvchemicals-oecd-org.lp.hscl.ufl.edu/ui/handler.axd?id=8785D1F3-5241-47AE-85C3-1505F707F9AF	Developmental Toxicity – Inhalation	-Pregnant New Zealand white rabbits (15/group) exposed to primary Amyl Acetate (65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate); 0, 500, 1000, 1500 ppm -6 h exposures; GD 6-18 -NOAEL for maternal toxicity determined to be 1000 ppm -NOAEL for developmental toxicity determined to be 1500 ppm	No developmental/reproductive toxicity data were available in the last report
Zeiger E, Anderson B, Haworth BS, et al. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen.1992; 19(Suppl. 21): 2-141	Genotoxicity – In Vitro	-Ames test on Isoamyl Acetate (up to 10 mg/plate) using *S typhimurium* -non-mutagenic	No

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
RIFM, 2007 *RIFM (Research Institute for Fragrance Materials, Inc.) Micronucleus Assay in Bone Marrow Cells of the Mouse with Isoamly Alcohol* *RIFM report number 54623* *RIFM, Woodcliff Lake, NJ, USA (2007)*	Genotoxicity – In Vivo	-Isoamyl Acetate in corn oil (500, 1000, and 2000 mg/kg bw) given to NMRI mice (5/sex/group) via gavage -non-mutagenic	No in vivo genotoxicity data were available in the last report
Api AM, Belsito D, Biserta S, et al. RIFM fragrance ingredient safety assessment, pentyl acetate, CAS Registry Number 628-63-7. Food Chem Toxicol. 2020; 14(Suppl 1): 111481.	RIFM Safety Assessment	-Amyl Acetate evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/ photoallergenicity, skin sensitivity, and environmental safety -The Expert Panel for Fragrance Safety concluded that this ingredient is safe as described in that safety assessment	This RIFM safety assessment was not published prior to the issuing of the CIR report. Amyl Acetate is not considered to be persistent, bioaccumulative, or toxic per IFRA Environmental Standards. This supports CIR's previous conclusion as safe as used for this ingredient.
Api AM, Belsito D, Botelho D, et al. RIFM fragrance ingredient safety assessment, Isoamyl Acetate, CAS Registry Number 123-92-2. Food Chem Toxicol. 2017; Dec;110 (Suppl 1) :S123-S132.	RIFM Safety Assessment	-Isoamyl Acetate evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitivity, and environmental safety -The Expert Panel for Fragrance Safety concluded that this ingredient is safe under the limits described in the safety assessment	This RIFM safety assessment was not published prior to the issuing of the CIR report. Isoamyl Acetate is not considered to be persistent, bioaccumulative, or toxic per IFRA Environmental Standards. This supports CIR's previous conclusion as safe as used for this ingredient.

Search (from 1982 on)
PubMed
(((“amyl acetate”) OR (628-63-7 [CAS NO.])) OR(211-047-3 [EC/RN Number])) AND (("1982"[Date - Publication] : "2022"[Date - Publication])) – 286 hits; 2 useful

OECD SIDS
(628-63-7 [CAS NO.]))

RIFM
(628-63-7 [CAS NO.]))

PubMed
(((“isoamyl acetate”) OR (123-92-2 [CAS Number])) AND (("1982"[Date - Publication] : "2022"[Date - Publication] AND (“toxicity”) OR (“allergy”) or (“inhalation” or “dermal”))

Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Amyl Acetate				**Isoamyl Acetate**			
	2022[1]	**1987[2]**	**2021[3]**	**1987[2]**	**2022[1]**	**1987[2]**	**2021[3]**	**1987[2]**
Totals*	**4**	**18**	**0.000000025 – 0.09**	**> 0.1 - ≤10**	**1**	**NR**	**0.002 – 0.22**	**NR**
Duration of Use								
Leave-On	*2*	*18*	*0.000000025 – 0.05*	*>0.1 - >10*	*1*	*NR*	*0.002 – 0.075*	*NR*
Rinse-Off	*2*	*NR*	*0.00004 – 0.09*	*NR*	*NR*	*NR*	*0.027 – 0.22*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*0.0078*	*NR*	*NR*	*NR*	*0.048*	*NR*
Exposure Type								
Eye Area	NR	NR	0.000000025	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	0.05; 0.03[a]	NR	1[a]	NR	0.0037 – 0.016	NR
Incidental Inhalation-Powder	NR	NR	0.026[b]	NR	NR	NR	0.019	NR
Dermal Contact	NR	NR	0.000000025 – 0.09	NR	1	NR	0.22	NR
Deodorant (underarm)	NR	NR	not spray: 0.0075 – 0.023; spray: 0.0032	NR	NR	NR	not spray: 0.0062 – 0.013; spray: 0.0065	NR
Hair - Non-Coloring	NR	NR	0.0012	NR	NR	NR	0.0037 – 0.082	NR
Hair-Coloring	NR	NR	0.0012 – 0.065	NR	NR	NR	NR	NR
Nail	4	18	NR	>0.1 - >10	NR	NR	NR	NR
Mucous Membrane	NR	NR	0.0031 – 0.09	NR	NR	NR	0.048 – 0.22	NR
Baby Products	NR	NR	NR	NR	NR	NR	0.008 – 0.075	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] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

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

NR – no reported use

References

1. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2022. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022). College Park, MD.

2. Elder RL. Final Report on the Safety Assessment of Amyl Acetate and lsoamyl Acetate. *J Am Coll Toxicol.* 1988;7(6).

3. Personal Care Products Council. 2022. Concentration of Use by FDA Product Category: Amyl Acetate and Isoamyl Acetate. (Unpublished data submitted to Personal Care Products Council on January 25, 2021.)

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1

Final Report on the Safety Assessment of Amyl Acetate and Isoamyl Acetate

Amyl Acetate, as used in cosmetic products, is the ester of mixed isomers of amyl alcohol and acetic acid. In cosmetic products, it is used as a solvent in fingernail formulations at concentrations of up to 10%.

Amyl Acetate can stimulate acetylcholine release in the nerve endings and act as a competitive inhibitor of acetylcholine in isolated nerves.

Amyl Acetate was not cytotoxic to diploid ascites tumors and was not a mitotic arrestant in cytogenetic studies. Amyl Acetate and Isoamyl Acetate were nonmutagenic in a series of mutagenic assays.

The acute oral toxicity of Amyl Acetate exceeds 5 g/kg. Only a low order of hepatotoxicity was reported following the intraperitoneal injection of 1.5 g/kg of Amyl Acetate in mature guinea pigs. No subchronic studies were available for Amyl Acetate; however, the results of subchronic studies of amyl alcohol in rats at concentrations up to 1 g/kg per day were unremarkable. Ocular studies of 100% Amyl Acetate in rabbits produced a conjunctival score of 6 (maximum 110) on day 1 that cleared by day 2.

No evidence of delayed contact hypersensitivity, phototoxicity, or photoallergy due to Amyl Acetate or Isoamyl Acetate was observed in human repeat insult patch test studies.

It is concluded that Amyl Acetate and Isoamyl Acetate are safe as presently used in cosmetic products.

INTRODUCTION

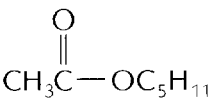
This report updates the available data on the toxicity of Amyl Acetate and Isoamyl Acetate since 1960. The reader is referred to the review by Von Oettingen[1] for earlier toxicologic test and use data.

CHEMISTRY

Definition and Structure

Amyl Acetate and Isoamyl Acetate as used in cosmetic products are the esters of mixed isomers of amyl alcohol and acetic acid that conform to the

general formula[1-3]:



Amyl Acetate (CAS No. 628-63-7) is also known as acetic acid, pentyl ester; acetic acid, amyl ester; amyl acetic ester; amyl acetic ether; *n*-amyl acetate; *n*-pentyl acetate; *pent*-acetate; *pent*-acetate 28; 1-pentyl acetate; pentyl acetate; 1-pentanol acetate; primary Amyl Acetate; Birnenoel; banana oil; and pear oil.[3-5]

Chemical and Physical Properties

Amyl Acetate is a colorless mobile liquid with a pear- or bananalike odor.[6,7] It is slightly soluble in water (0.25% w/w) and highly soluble in alcohol, ether, and other common organic solvents.[3,8-11] The compound is flammable.[7,10,12,13] Amyl Acetate can react with oxidizing materials,[7] is subject to hydrolysis by strong acids or alkalies,[3] and is reported "incompatible" with nitrates and strong oxidizers.[6]* Under normal cosmetic use, the ester can be expected to be stable.[3] Additional chemical and physical data are presented in Table 1.

Natural Occurrence and Method of Manufacture

Amyl Acetate occurs naturally in various fruits, such as the volatile aroma of banana oil, where it is biosynthesized from L-leucine.[14] The compound has also been identified in yeast[15] and honeybees.[16]

The cosmetic ingredient is synthesized for commercial use by the esterification of amyl alcohol (mixed isomers) with acetic acid.[3,8,10] The ingredient may subsequently undergo distillation and purification.[3] One available commercial product has a minimum purity of 98%.[17] An average of over 100 production analyses of a Union Carbide primary Amyl Acetate (mixed isomers, *n*-pentyl acetate, and 2-methyl butyl acetate) is shown in Table 2. These data were obtained using a packed-column gas chromatograph (GC) on a water-free basis. The minimum specification of this ingredient (*n*-pentyl acetate plus 2-methyl butyl acetate) is 98.0%. The material identified as *n*-pentanol could also contain some *n*-butyl acetate. These peaks elute together on the GC.[18]

Analytic Methods

Analytic methods for the determination of Amyl Acetate include gas-liquid chromatography and mass spectroscopy.[3,6,17,21-24]

*Mackison et al. (1978) refer to "incompatible" as a "potentially hazardous" incompatibility.[6]

TABLE 1. Chemical and Physical Data for *n*-Amyl Acetate[a]

Data	*Description*	*References*
Appearance	Colorless liquid	6–8,10
Molecular formula	$CH_3COO(CH_2)_4CH_3$	7,17
Molecular weight	130.191	3,9,11
Assay[a]		
Total esters	Not less than 98%	3
Isoamyl Acetate	20.0–37.0%	
n-Pentyl acetate	62.0–78.0%	
Melting point	−70.6°C	6
	−70.8°C	8–11
	−78.5°C	7
Boiling point	137–142°C	19
	140–150°C	3
	146°C at 760 mm Hg	6,17
	148°C at 737 mm Hg	7
	148.4°C	10
	148.8°C	8
	149.25°C	9,11
Flash point	77°F (closed cup)	6,7,9,10
	105°F (closed cup)	8
Autoignition temperature	714°F	7,8,10
Lower explosive limit	1.1% by volume	6,7,9
Upper explosive limit	7.5% by volume	6,7,9
Saponification value	427–432	3
Vapor pressure	4 mm Hg at 20°C	6,8
Vapor density	4.5	7,9
Specific gravity (density)	0.874–0.879 (d_4^{25})	3
	0.8756 at 20/40°C	9,11
	0.879 at 20/20°C	7,8,10
Refractive index (η_D)	1.4023 at 20°C	9,11
	1.399–1.403 at 20°C	3
Weight per gallon	7.22 pounds at 20°C	10
Solubility in water	0.2% (g per 100 g water at 20°C)	3,6
Evaporation coefficient[b]	13.0	19
Acidity (as acetic acid)	0.01% maximum	3
Weight-volume conversion	5.31 mg/m^3 = ~ 1 ppm	9
Partition coefficient in an iso-octane:water system	9.8	20

[a]Amyl Acetate is a commercially available blend of 1-pentyl acetate and Isoamyl Acetate.[3]

[b]The evaporation coefficient is based on the evaporation rate of a standard volume of ethyl ether. Amyl Acetate was allowed to evaporate under uniform conditions, and the time required for complete evaporation of a standard volume was then compared with that of a sample of ethyl ether.[19]

TABLE 2. Production Analyses of Amyl Acetate

n-Pentyl acetate	64.84%
2-Methyl butyl acetate	34.57
Subtotal (primary Amyl Acetate)	99.41%
Major impurities	
n-Pentanol	0.26%
2-Methyl butanol	0.20
2-Methyl butyl formate	0.01
Other lights and heavies, all single components less than 0.01	0.12
	100%

Source: From Reference 18.

COSMETIC USES

Amyl Acetate is used in cosmetics primarily as a solvent for nitrocellulose in nail polishes, enamels, and lacquers and also functions as a solvent in nail enamel removers.[3,19]

In enamel removers, Amyl Acetate may be used in combination with other solvents, like acetone or ethyl acetate. Small amounts of fatty material (butyl stearate, dibutyl phthalate, fatty alcohols, and soaps) may be incorporated into the enamel remover to counteract the excessive drying action of the solvents on the nails.[19]

Data submitted to the Food and Drug Administration (FDA) in 1987 by cosmetic firms participating in the voluntary cosmetic registration program indicated that Amyl Acetate was used in a total of 18 cosmetic products (Table 3). Product types formulated with Amyl Acetate included nail basecoats and undercoats (3 products) nail polish and enamel (11 products), and other manicuring preparations (4 products). Concentrations of Amyl Acetate in these products were as follows: > 5–10% (4 products), > 1–5% (12 products), and > 0.1–1% (2 products).[25]

Voluntary filing of product formulation data with the FDA by cosmetic manufacturers and formulators conforms to the format of concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations.[26] Because the data are submitted only within the frame-

TABLE 3. Product Formulation Data for Amyl Acetate

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*		
			> 5–10	> 1–5	> 0.1–1
Basecoats and undercoats	36	3	1	2	
Nail polish and enamel	151	11	2	8	1
Other manicuring preparations	41	4	1	2	1
1987 Totals		18	4	12	2

Source: From Reference 25.

work of preset concentration ranges, opportunity exists for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration.

Cosmetic products containing Amyl Acetate are typically applied to the nails or to the skin. During application of these products, Amyl Acetate may come in contact with nasal mucosa, lungs, and eyes as a result of evaporation from the formulation. Cosmetics formulated with this solvent have the potential for repeated application over the course of many years.

NONCOSMETIC USES

Amyl Acetate is used as a solvent in lacquers, paints, leather polishes, inks, adhesives, thinners, and degreasers and functions as a solvent for phosphors in fluorescent lamps. It is also used in cement, photographic film, and printing and finishing fabrics.[8,10,27,28] Federal regulations permit the use of Amyl Acetate as a component of adhesives used in food packaging articles. No limitations have been established for this indirect food additive use.[29] In research, Amyl Acetate is used as a partition solvent,[30] as a component of buffer mixtures for antibiotic-DNA binding,[30] as a weevil attractant,[31] as an anti-inflammatory agent,[32] and as an odorant.[33-41]

Although Amyl Acetate is not listed in the Code of Federal Regulations as an approved natural or synthetic food flavoring substance,[42,43] it is reportedly used as a flavoring agent.[8,10]

BIOLOGY

Effect on Cholinergic Nerve Structure and the Acetylcholine Receptor

The effect of various acetates on the cholinergic nerve structure and the acetylcholine receptor of guinea pig ileum was studied by Takagi and Takayanagi.[44] Amyl Acetate produced contractions of isolated guinea pig ileum by liberating acetylcholine from the cholinergic nerve endings. Contractions of the ileum following acetate exposure were inhibited by atropine, procaine, and cooling, suggesting that the site of action of agonistic acetates may be within the nerve structure. Amyl Acetate also acted as a competitive inhibitor of acetylcholine when it was "combined with" the acetylcholine receptor on the muscle.

Anti-inflammatory Effects

The anti-inflammatory effects of Amyl Acetate were assessed in the rat paw carrageenan response test. Inflammation was induced by subcutaneous injection of carrageenan (1 mg in 0.1 ml normal saline) into the right hindpaws of six Wistar rats. Amyl Acetate dissolved in polysorbate 80 was administered intraperitoneally 30 minutes before the inflammatory stimulus. The percentage

inhibition of inflammation was calculated by comparing the mean percentage increase in the paw volume of the control group with the paw volume of the treated group. After 3 h a dose of 100 mg/kg of Amyl Acetate inhibited inflammation nearly 22%.[32]

Antihemolytic Effects

The antihemolytic effect of Amyl Acetate and other organic solvents was investigated in vitro using rat erythrocytes. Addition of 350 pm (2.37 mM) Amyl Acetate to an erythrocyte-saline buffer suspension reduced hypotonic hemolysis by 50% relative to control cells. Amyl Acetate concentrations of >1000 ppm (>6.77 mM) afforded 100% protection against hemolysis. The antihemolytic effect was evident only when the solvent molecule was present during the hemolytic process. Antihemolysis was associated with an increase in the critical cell volume of the erythrocytes, indicating the protective effect was related to a solvent-induced increase in membrane stability of the red blood cells. A correlation was observed between the antihemolytic potency of the various organic solvents examined and their partition coefficients in an iso-octane:water system.[20]

Cytotoxicity

Amyl Acetate was not cytotoxic to Ehrlich-Landschutz diploid ascites tumor cells at incubation media concentrations of 50 or 100 ppm Amyl Acetate.[45]

Amyl Acetate was not mitostatic in cytogenetic studies using the grasshopper embryo assay system.[46]

METABOLISM

No data were available on the metabolism of Amyl Acetate. However, the metabolism of esters similar to Amyl Acetate suggest that this ingredient undergoes enzymatic hydrolysis to form acetic acid and amyl alcohol.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

The acute oral toxicity (LD_{50}) of Amyl Acetate for rabbits is 7.4 g/kg[7] and ranges from 5 to 16.6 g/kg for rats.[47,48]

Ocular Irritation

In a rabbit eye irritation test, undiluted Amyl Acetate received a rating of 2 on a scale of 1–10.[47]

A Draize eye irritation test of 100% Amyl Acetate using three rabbits produced a maximum conjunctival score of 6 (maximum 110) on day 1. The

eye was normal on day 2. No irritation was noted in the cornea or iris. The contralateral eye was used as the untreated control.[49]

A suntan lotion containing 0.2% Amyl Acetate was evaluated for eye irritation potential. The product was instilled in a single 0.1 ml dose into the conjunctival sac of six female New Zealand white rabbits. The treated eyes of three of six rabbits received a water rinse following exposure. No ocular reactions were reported in the treated, either rinsed or unrinsed, rabbit eyes.[50]

Skin Irritation and Sensitization

Smyth et al.[47] reported that undiluted Amyl Acetate produced only the least visible capillary injection when tested on the clipped skin of five albino rabbits.

Amyl Acetate, described as a mixture of the isomeric forms of pentyl acetate, was investigated for its potential to cause allergenic contact dermatitis using a guinea pig maximization procedure. It was considered a possible marginal skin sensitizer for the guinea pig.[51]

Intraperitoneal Injection

The hepatotoxicity of Amyl Acetate was evaluated in mature male guinea pigs. The undiluted cosmetic ingredient was given by intraperitoneal injection at dose of either 0.75 or 1.5 g/kg to two groups consisting of four animals each. Serum ornithine carbamyltransferase (OCT) activities were measured 24 h after injection and the livers were removed for histopathologic examination. Untreated control animals had a serum OCT activity of 2.02 ± 1.61 IU (range = 0–8.9). In the four guinea pigs of the 750 mg/kg group, serum OCT was elevated to an average of 10.2 IU. At microscopic examination, neither necrosis nor lipid was found in the liver. In the 1500 mg/kg group, three of four animals died. Serum OCT of the surviving guinea pig was elevated to 11.7 IU. Although hepatic necrosis was absent from the high-dose group, hepatic lipid deposition was moderate. The authors concluded that Amyl Acetate had a relatively "low" order of hepatotoxicity.[52]

Inhalation Toxicity

Smyth et al.[47] found that air nearly saturated (approximately 5200 ppm) with technical-grade Amyl Acetate was fatal to six of six rats after 8 h of exposure, but no rats died after an exposure period of 4 h.[8]

Cats exposed by inhalation to 2200 ppm Amyl Acetate for 3.5 h and 10,600 ppm for 1 h had increased salivation. Lacrimation and irregular respiration occurred at the higher exposure after 1 h, and a loss of reflexes occurred after 1.5 h.[1,9] Narcosis was observed in rats exposed by inhalation for 0.5 h to 5000 ppm Amyl Acetate.[7]

The results of inhalation studies are summarized in Table 4.

TABLE 4. Inhalation of Amyl Acetate

Animal	*Amyl Acetate concentration (ppm)*	*Exposure time (h)*	*Effects*	*Reference*
Rat	5,200	8	Fatal to six of six rats in 8 h but caused no deaths in 4 h	47,8[a],9[a]
Cat	2,182	3.5	Increased salivation	1,9[a]
Cat	5,000	0.5	Narcosis	7[a]
Cat	10,600	2.0	Marked salivation, lacrimation, irregular respiration; loss of reflexes after 85 minutes	1,9[a]

[a]Secondary references.

Subchronic Toxicity

No subchronic data were available on Amyl Acetate; however, data were available on *n*-amyl alcohol. Since *n*-amyl acetate and *n*-amyl alcohol have similar solubilities in water, the rates of absorption and excretion and the volumes of distribution for the two compounds are likely to be the same. In addition, *n*-amyl acetate is likely to be metabolically hydrolyzed to *n*-amyl alcohol (and acetic acid); therefore, the subchronic toxicity of *n*-amyl alcohol is likely to be similar to that of *n*-amyl acetate.

n-Amyl alcohol, dissolved in corn oil, was administered to ASH/CSE strain rats by oral intubation at dose of 0, 50, 150, or 1000 mg/kg per day of *n*-amyl alcohol for 13 weeks. The *n*-amyl alcohol was dissolved in the corn oil in appropriate concentrations so that all animals received a dosage volume of 5 ml/kg per day. Test and control groups each consisted of 15 male and 15 female rats. No differences were observed between treated and control rats with respect to appearance, behavior, or feed and water consumption. All animals "appeared healthy" throughout the study. The amyl alcohol treatment "had no demonstrable effect" on body weight gain, hematologic values, results of serum and urine analyses, renal function, organ weights, or organ microstructure. Isolated differences between control and treated rats were noted in the results of hematologic studies. The investigators found no consistent pattern in any of the hematologic findings with respect to dose-response, sex, or time relationships. The results of the serum analyses were similar in test and control rats. In all groups, the urine was free of bile, blood, glucose, and ketones. The concentration of albumin was similar in all groups. At week 6, cell counts were lower in the urine of the male rats given 150 or 1000 mg/kg per day; the differences were statistically significant. Some statistically significant differences were also noted in the concentration tested at week 12; the specific gravity of the samples collected at 16–20 h from females given 1000 mg/kg per day was higher than the control value and the volume was lower. After the same period, the male rats given 50 or 1000 mg/kg per day produced less urine in the 6 h period without water. Relative to body weight, the spleen from the female rats dosed with 1000 mg/kg per day had a low value, as did the renal weights of females, both at this and at the 150 mg/kg per day dose. At necropsy, no visible abnormalities were observed at

any dose. On microscopic examination, protein casts and foci of calcification were noted in the renal tubules, but the incidences were similar in the treated animals and their corresponding controls. The incidence of fatty change and inflammatory cell infiltration in the liver were also comparable in the control and treated rats. The authors reported that "all the tissues" were examined grossly and that the following organs were weighed: brain, heart, liver, spleen, kidneys, stomach, small intestine, cecum, adrenal glands, gonads, pituitary gland, and thyroid gland. Samples of these organs and of the lungs, lymph nodes, salivary glands, trachea, esophagus, aortic arch, thymus, urinary bladder, colon, rectum, pancreas, uterus, and skeletal muscle were examined microscopically. Urine analyses included tests for volume, specific gravity, appearance, number of cells, and content of albumin, glucose, ketone, bile salts, and blood. Serum was analyzed for urea, glucose, total protein, and albumin, as well as for the activities of glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, and lactic dehydrogenase. Hematologic studies included analyses of hemoglobin concentration, packed cell volume, erythrocyte and leukocyte counts, and differential leukocyte counts. Based upon all the data, the authors concluded that the "no-effect" level for *n*-amyl alcohol in the rat is, like that for isoamyl alcohol, at least 1000 mg/kg per day.[53]

Mutagenicity

Amyl Acetate was not a mutagen in the Ames assay, either with or without metabolic activation in *Salmonella typhimurium* strains TA-1538, TA-98, TA-1535, TA-100, and TA-1537.[49]

Isoamyl Acetate was negative for mutagenesis in the recombinant assay test in *Bacillus subtilis* M45 (*rec*$^-$) and H17 (*rec*$^+$) strains.[54] Isoamyl Acetate was also negative for mutagenesis when tested in *Saccharomyces cerevisiae* strain D61.M.[55] No mutagenicity was found when Isoamyl Acetate was tested in the Ames reverse mutation assay using *S. typhimurium* strains TA-1538, TA-98, TA-1535, TA-100, and TA-1537, both with and without metabolic activation. The Chinese hamster chromosomal abberation assay was also negative.[56] Isoamyl Acetate was also nonmutagenic in a combined study using the Ames, *Escherichia coli*, and *B. subtilis* DNA repair, as well as in the mouse lymphoma forward mutation assay.[57]

CLINICAL ASSESSMENT OF SAFETY

Human Skin Sensitization

A repeat insult patch test of 20% Isoamyl Acetate and 20% Amyl Acetate was conducted using a panel of 211 male and female subjects. A total of 197 subjects completed the study. A vehicle control, 75% ethanol and 25% diethyl phthalate, was also included in the testing program. The test material, 0.3 ml, was applied to a Webril patch and allowed to volatilize for 15 minutes before applying the patch to the skin site. The patch remained on the skin for 24 h before removal. The sites were evaluated and fresh patches applied three

times per week for 3 weeks. The sites were evaluated at 48 and 96 h after application throughout the treatment period. Following a 10–15 day nontreatment period, the subjects were given a challenge patch using the same dose and contact period as used during the induction phase of the study. No evidence of delayed-contact hypersensitivity was observed, and no adverse reactions were observed during the entire exposure period to either Amyl or Isoamyl Acetate.[58]

A repeat insult patch test was conducted with 208 panelists to determine the irritation potential of a suntan lotion containing a reported 0.1% Amyl Acetate. The product was applied under an occlusive patch for 48 h to the skin of the back. Induction applications were made on Monday, Wednesday, and Friday for three consecutive weeks. Following a 2 week nontreatment period, two consecutive 48 h challenge patches were applied to a site adjacent to the induction site. Skin responses were evaluated 48 and 96 h following treatment. Of the 208 subjects, 19 developed ± reactions on challenge. The investigator reported that these ± reactions were "due to irritant response to TEA stearate emulsions under occlusion." The suntan lotion appeared to have "little potential for sensitization." Irritation reactions from the induction phase were not reported. To further evaluate the results of this study, results from a separate repeat insult patch test were presented by the investigator. In this second study, 155 subjects were treated with a TEA stearate lotion "with a different fragrance" and "0.18%" Amyl Acetate. Of the total, 11 subjects had reactions on challenge: 9 of 155 developed macular, faint erythema, and 2 of 155 developed moderately intense erythema.[59]

Phototoxicity and Photoallergy

A human phototoxicity test of 30% *n*-amyl acetate solution was conducted using a panel of 25 subjects of whom 23 completed the study. The material, 0.3 ml, was applied to separate areas of the back under occlusive Webril patches for 24 h. The sites to be evaluated for photoxicity were irradiated with 16–20 J/cm^2 of UV-A (ultraviolet-A) light within 10 minutes of patch removal. The sites were evaluated at 1, 24, 48, and 72 h postirradiation. No indication of phototoxicity and/or primary irritation was observed.[60]

A human photoallergy and primary phototoxicity test of 20% Amyl Acetate and 20% Isoamyl Acetate was conducted using a panel of 25 subjects. During the induction period the treatment sites were evaluated and fresh patches applied two times per week for 3 weeks. UV-B irradiation (26–32 mW/GM^2) was also applied during the biweekly evaluation periods. In addition, each subject received approximately 4 J UV-A. Following a 2 week nontreatment period, the sites were exposed to UV-A, 16–20 J/cm^2, for evaluation of photosensitization; a separate nonexposed site was evaluated for contact sensitization. Neither Amyl Acetate nor Isoamyl Acetate produced a phototoxic or photoallergenic response in the subjects tested.[60]

EXPOSURE OF HUMANS TO AIRBORNE CONCENTRATIONS

Symptoms in humans following inhalation of Amyl Acetate or following exposure to Amyl Acetate vapors may include mucous membrane irritation,

headache, fatigue, excessive salivation, "oppression" in the chest, lacrimation, nose and throat irritation, and occasional vague nervousness.[6,8,9]

The odor detection threshold for Amyl Acetate (> 99% purity) was measured in 23 subjects during two sessions by means of an olfactometer. The mean olfactory detection threshold was 0.18 ± 0.03 ppm. The detection threshold for each individual was defined as "the lowest concentration above which the subject detected the odor at each presentation in both runs."[36]

Eye, nose, and throat irritation following exposure to Amyl Acetate vapors was assessed in humans. Groups of 10 subjects of both sexes were individually placed in a 1200 foot^3 exposure chamber and exposed to various concentrations of Amyl Acetate vapor. Following each 3–5 minute exposure, subjects classified the degree of irritation of the eyes, nose, and throat. Amyl Acetate caused "mild" eye and nose irritation and "severe" throat irritation at 200 ppm. "Slight throat discomfort" was experienced at 100 ppm.[61]

The American Conference of Governmental Industrial Hygienists[8,62] has adopted the following airborne threshold limit values for Amyl Acetate to prevent irritation of the eyes and respiratory passages: (1) threshold limit value, time-weighted average, 100 ppm (530 mg/m^3); (2) threshold limit value, short-term exposure limit, 150 ppm (800 mg/m^3).

An airborne concentration of 4000 ppm Amyl Acetate is classified by the NIOSH-OSHA Standards Completion Program as "immediately dangerous to life or health."[6] An airborne concentration of 5000 ppm Amyl Acetate is classified by the NIOSH Registry of Toxic Effects of Chemical Substances as a "toxic concentration."[5] Sac[7] reports that exposure by inhalation to an Amyl Acetate concentration of 188 ppm for 30 minutes was toxic to humans.

SUMMARY

Amyl Acetate, as used in cosmetic products, is the ester of mixed isomers of amyl alcohol and acetic acid. In cosmetic products, it is used as a solvent in fingernail formulations at concentrations up to 10%.

Amyl Acetate can stimulate acetylcholine release in the nerve endings and act as a competitive inhibitor of acetylcholine in isolated nerves. Anti-inflammatory and antihemolytic effects of Amyl Acetate have also been reported.

Amyl Acetate was not cytotoxic to Ehrlich-Landschutz diploid ascites tumors at concentrations up to 100 ppm, and it was not a mitotic arrestant in cytogenetic studies using a grasshopper embryo assay system. Ayml Acetate was nonmutagenic, with and without metabolic activation, in the Ames assay using *S. typhimurium*. Isoamyl Acetate was not mutagenic in either the *B. subtilis* recombination assay system or the *S. cerevisiae* mutagenesis assay system.

The acute oral toxicity of Amyl Acetate exceeds 5 g/kg. Only a low order of hepatotoxicity was reported following intraperitoneal injection of 1.5 g/kg of Amyl Acetate in mature guinea pigs. Although no subchronic studies have been reported for Amyl Acetate, the results of subchronic studies of amyl alcohol in rats at concentrations up to 1 g/kg per day were unremarkable.

Because of the chemical and physical similarities of *n*-amyl acetate and *n*-amyl alcohol, the biologic responses following exposure to *n*-amyl alcohol support the safety evaluation of *n*-amyl acetate.

Ocular studies of 100% Amyl Acetate in rabbits using a Draize procedure produced results of a maximum conjunctival score of 6 (maximum 110) on day 1 that cleared by day 2. No irritation of the cornea or iris was observed. A formulation containing 0.2% Amyl Acetate was not an eye irritant in treated, either rinsed or unrinsed, rabbit eyes.

Undiluted Amyl Acetate produced only slightly visible capillary injection when tested on rabbits and was only a "possible marginal sensitizer" when tested using guinea pigs and a maximization procedure.

Repeat insult patch tests of a formulation containing 0.1% Amyl Acetate were inconclusive about the sensitization by this ingredient. However, no evidence of delayed-contact hypersensitivity due to 20% Amyl Acetate or 20% Isoamyl Acetate was observed in repeat insult patch test studies using 211 human subjects. No evidence of phototoxicity was observed when 30% Amyl Acetate was tested using a panel of 23 subjects. There was no indication of phototoxicity or photoallergy when 20% Amyl Acetate and/or 20% Isoamyl Acetate was tested using a panel of 23 subjects.

CONCLUSION

On the basis of the information included in this report, the CIR Expert Panel concludes that Amyl Acetate and Isoamyl Acetate are safe as presently used in cosmetic products.

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