ISOPROPANOLAMINES

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published the Final Report on the Safety Assessment of Diisopropanolamine, Triisopropanolamine, Isopropanolamines, and Mixed Isopropanolamines in 1987.[1] The Panel concluded that these 4 ingredients are safe as cosmetic ingredients in the present practices of use and concentration (as described in the safety assessment); these ingredients should not be used in products containing *N*-nitrosating agents. The Panel previously considered a re-review of this report in December 2004, and re-affirmed the 1987 conclusion, as published in 2006.[2]

Because it has been at least 15 years since the re-review was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel considered whether the safety assessment should be reopened. At the September 2024 meeting, the Panel reviewed updated (2023) information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database[3] and maximum use concentrations provided in response to the survey conducted by the Personal Care Products Council.[4] Overall, the reported frequency and concentrations of use for these ingredients have decreased since the previous review. In 2002, Diisopropanolamine was reported to be used in 33 formulations, with 1 reported use in 2023. The maximum reported concentrations of use in 2004 were 1% Isopropanolamine in hair dyes and colors and 1% Triisopropanolamine in a pump hair spray; the maximum reported concentration of use in 2023 was 0.85% Triisopropanolamine in non-spray tonics, dressings, and other hair grooming aids. Mixed Isopropanolamines did not have reported uses in 2002/2024 or 2023. The cumulative frequency and concentration of use data are presented in Table 1.

In August 2024, an extensive search of the world's literature was performed for studies dated 2001 forward. Considerable new data were found, including data on toxicokinetics, acute toxicity, repeated-dose toxicity, developmental and reproductive toxicity, in vitro genotoxicity, carcinogenicity, dermal irritation and sensitization, ocular irritation, clinical studies, and case reports. The Panel concluded these new data served to reaffirm the existing conclusion of safety; accordingly, this safety assessment was not reopened. However, they acknowledged the importance of capturing this information robustly, and therefore these studies are summarized in Tables 2 – 12.

Furthermore, the Panel discussed the possibility for these ingredients to be used in cosmetic products which may be incidentally inhaled. 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. Some products containing these ingredients may be marketed for use with airbrush delivery systems; however, this information is not available from the VCRP or the Council survey. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

In summary, the Panel reviewed 2023 frequency and concentration of use data, in addition to any new relevant safety data. After considering this information, as well as the information provided in the original safety assessment, the Panel reaffirmed the 1987 conclusion for the isopropanolamines stating that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration, and that these ingredients should not be used in products containing *N*-nitrosating agents.

Table 1. Frequency (2023/2002) and concentration (2023/2004) of use according to likely duration and exposure and by product category

	Diisopropanolamine				Isopropanolamine				Triisopropanolamine			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]
Totals*	**1**	**33**	**0.003 – 0.5**	**0.01 – 0.7**	**3**	**27**	**0.015 – 0.11**	**1**	**12**	**25**	**0.000066 – 0.85**	**0.4 – 1**
summarized by likely duration and exposure**												
Duration of Use												
Leave-On	*NR*	*21*	*0.003 – 0.5*	*0.7*	*1*	*27*	*0.11*	*NR*	*11*	*22*	*0.000066 – 0.85*	*0.4 - 1*
Rinse-Off	*1*	*12*	*NR*	*0.01*	*2*	*NR*	*0.015 – 0.016*	*1*	*1*	*3*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type*												
Eye Area	NR	NR	NR	NR	NR	23	NR	NR	3	NR	0.00031 – 0.0004	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	11; 6[a]	0.003 – 0.17	0.7[a]	NR	3[a]; 1[c]	NR	NR	8[a]	9; 12[a]	0.000066 – 0.51; 0.5[a]	0.4-1; 0.7[a]
Incidental Inhalation-Powder	NR	NR	0.5[b]	NR	NR	1[c]	0.11[b]	NR	NR	NR	0.0002[b]	NR
Dermal Contact	NR	19	0.03 – 0.5	0.01	1	4	0.11	NR	4	NR	0.0002 – 0.0004	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	11	0.003	0.7	1	1	0.016	NR	8	25	0.000066 – 0.85	0.4 – 1
Hair-Coloring	NR	3	NR	NR	1	NR	0.015	1	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR	NR	NR	NR	NR
as reported by product category												
Baby Products												
Other Baby Products					1	NR	NR	NR				
Eye Makeup Preparations												
Eyebrow Pencil									NR	NR	0.00031	NR
Eyeliner					NR	1	NR	NR				
Mascara					NR	22	NR	NR				
Other Eye Makeup Preparations									3	NR	0.0004	NR
Fragrance Preparations												
Cologne and Toilet Water	NR	1	NR	NR								
Other Fragrance Preparation	NR	10	NR	NR								
Hair Preparations (non-coloring)												
Hair Conditioner	NR	1	NR	NR					1	NR	NR	NR
Hair Spray (aerosol fixatives)	NR	NR	pump spray: 0.003	NR					NR	9	aerosol: 0.000066 – 0.51	0.4
Permanent Waves	NR	3	NR	NR								
Shampoos (non-coloring)	1	NR	NR	NR	1	NR	0.016	NR				
Tonics, Dressings, and Other Hair Grooming Aids	NR	5	NR	0.7	NR	1	NR	NR	7	12	spray: 0.5 not spray: 0.85	0.7
Wave Sets	NR	1	NR	NR					NR	3	NR	NR
Other Hair Preparations	NR	1	NR	NR					NR	1	NR	pump spray: 1
Hair Coloring Preparations												
Hair Dyes and Colors (all types requiring caution statements and patch tests)	NR	3	NR	NR	NR	NR	0.015	1				
Hair Tints					1	NR	NR	NR				
Shaving Preparations												
Aftershave Lotion	NR	2	NR	NR								

Table 1. Frequency (2023/2002) and concentration (2023/2004) of use according to likely duration and exposure and by product category

	Diisopropanolamine				Isopropanolamine				Triisopropanolamine			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]
Other Shaving Preparations	NR	3	NR	NR								
Skin Care Preparations												
Cleansing	NR	NR	NR	0.01								
Face and Neck (exc shave)	NR	NR	not spray: 0.5	NR					NR	NR	not spray: 0.0002	NR
Body and Hand (exc shave)	NR	NR	not spray: 0.5 spray: 0.17	NR	NR	1	not spray: 0.11	NR				
Moisturizing					NR	1	NR	NR	1	NR	NR	NR
Paste Masks (mud packs)	NR	1	NR	NR								
Skin Fresheners	NR	1	NR	NR								
Other Skin Care Preparations	NR	1	NR	NR								
Suntan Preparations												
Suntan Gels, Creams, and Liquids	NR	NR	not spray: 0.03	NR	NR	1	NR	NR				

NR – not reported
*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.
**likely duration and exposure are derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
[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.
[c] 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

Table 2. EU regulations[8]

Ingredient	EU Regulation	Restriction
Diisopropanolamine	EC No 1223/2009 Annex II	Reaction products of Diisopropanolamine with formaldehyde (1:4) are prohibited for use in cosmetic products.
Diisopropanolamine	EC No 1223/2009 Annex II	Secondary alkyl- and alkanolamines and their salts are prohibited for use in cosmetic products.
Isopropanolamine	EC No 1229/2009 Annex III	Monoalkylamines, monoalkanolamines, and their salts may not be used with nitrosating systems, must have a minimum purity of 99%, a maximum secondary amine content of 0.5% (applies to raw materials), a maximum nitrosamine content of 50 µg/kg, and must be kept in nitrite-free containers.
Triisopropanolamine	EC No 1229/2009 Annex III	Trialkylamines, trialkanolamines, and their salts may not be used at concentrations greater than 2.5% in leave-on products, may not be used with nitrosating systems, must have a minimum purity of 99%, a maximum secondary amine content of 0.5% (applies to raw materials), a maximum nitrosamine content of 50 µg/kg, and must be kept in nitrite-free containers.

Table 3. Absorption, distribution, metabolism, and excretion studies

Test Article	Vehicle	Animals	Concentration/Dose	Protocol	Results	Reference
^{14}C-labelled Triisopropanolamine salt (concomitantly with 2,4-dichlorophenoxyacetic acid)	water	4 male Fischer 344 rats	10.7 mg/kg bw	OECD TG 417; single gavage administration	Approximately 80% of the radioactivity was excreted in urine within the first 24 h post-dosing; 81 – 85% was excreted by 72 h. Feces accounted for 4 – 7% and expired $^{14}CO_2$ accounted for 3 – 5% of the excreted dose. Less than 1% of the radioactive dose remained in the tissues and carcass of rats that were killed 72 h post-dosing.	[9]

Abbreviations: OECD - Organisation for Economic Co-operation and Development; TG - test guideline

Table 4. Acute toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
Diisopropanolamine	none	male New Zealand white rabbits (4/group)	100%; 0, 4000, 8000, or 16,000 mg/kg	occlusive applications; 24-h patches; application to intact skin	LD_{50}: 8000 mg/kg bw Two animals in the 8000 mg/kg group and all animals in the 16,000 mg/kg group died; erythema and necrosis was observed at all dose levels; congestion of lungs, livers, spleens, and kidneys, mottled livers, and opaque stomachs were also observed (dose at which these effects were seen not specified).	[10]
ORAL						
Diisopropanolamine	olive oil	Wistar rats (5/sex/group)	0, 1000, or 2000 mg/kg bw	OECD TG 401; single oral dose; gavage	LD_{50} > 2000 mg/kg bw	[10]
Diisopropanolamine	water	rats (5/sex/group)	200, 1600, 3200, or 6400 mg/kg bw	single dose of 200, 1600, 3200, or 6400 mg/kg bw; gavage	LD_{50} approximately 6000 mg/kg bw in 6400 mg/kg bw group: respiration; dilated stomach and intestinal irritation in 3200 mg/kg group: 1 female died within first 24 h	[10]
INHALATION						
nebulized Isopropanolamine (MMAD ≥ 1 - ≤ 2 μm);	air	male Swiss Webster mice (4/group)	230 – 1005 mg/m^3	OECD TG 403; nose/head-only, 3-h exposure to nebulized test substance; animals given 20 min recovery period	LC_0 > 1005 mg/m^3 RD_{50}: 440 mg/m^3; post-exposure recovery of the respiratory frequency was moderate to good no mortality occurred; mild sensory and pulmonary irritation observed (assessed via measurement of decreased respiratory frequency)	[11,12]
aerosolized Isopropanolamine	air	male Fischer 344 rats (number not specified)	1126 ppm (3460 mg/m^3)	OECD TG 403; 6-h exposure; 14-d observation period	LC_{50} > 1126 ppm (3460 mg/m^3)	[11]
vaporized Isopropanolamine	air	rats (6/sex/group; strain not specified)	1.95 mg/l	OECD TG 403; 8-h exposure; 7-d observation period	LC_0 calculated: 610 ppm No mortality or abnormalities were observed	[11]

Abbreviations: LC_0 - maximum tolerable concentration; LC_{50} - median lethal concentration; LD_{50} - median lethal dose; MMAD - mass median aerodynamic diameter; OECD - Organisation for Economic Co-Operation and Development; RD_{50} - concentration capable of evoking a 50% decrease in mean breathing frequency; TG - test guideline

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
DERMAL							
Diisopropanolamine	NR	Fischer 344 rats (5/sex/group)	4 wk	0, 100, 500, or 750 mg/kg/d	test substance applied under occlusive conditions to a clipped 2 cm^2 area for 6 h/d, 5 d/wk for 4 wk	During the course of the study, slight erythema was noted in 2 males and 2 females from the 500 mg/kg/d group, all 750 mg/kg males, and three 750 mg/kg females. Erythema and scabs were mostly noted from day 19 onwards for males and females in the 500 and 750 mg/kg/d groups. Very slight hyperkeratosis occurred in 2 males and 2 females in the 500 mg/kg/d group and slight hyperkeratosis occurred at the test site of all rats in the 750 mg/kg/d group. On day 26, light fissuring and scales were seen in 2 females from the 750 mg/kg/d group. No adverse dermal effects observed in the 100 mg/kg/d group. No systemic or treatment-related effects upon hematology, urinalysis, body and organ weight, or gross pathology were noted.	13
Triisopropanolamine	distilled water	Fischer 344 rats (5/sex/group)	28 d	0, 7.5, 25, or 75% (corresponding to 0, 300, 1000, and 3000 mg/kg bw/d, respectively)	OECD TG 410; animals administered test substance under semi-occlusive conditions 5 d/wk for 28 d (patches applied for 6 h); negative controls treated with distilled water	NOAEL (systemic toxicity): ≥ 3000 mg/kg bw/d Triisopropanolamine NOAEL (local toxicity): 300 mg/kg bw/d (based on dermal irritation) Slight erythema and scabs were observed at the test sites of 2 male rats in the 1000 mg/kg group. From the 3000 mg/kg group, similar results were seen in 2 males on day 4 (resolved by day 11), 3 male rats on day 18 (resolved by day 28), and 1 female rat on day 25 (still present at day 28). Microscopically, 2 males and 1 female from the 1000 mg/kg bw/d group also exhibited very slight epidermal hyperplasia, asdid 1 control female. Epidermal hyperplasia was observed at treatment sites for 3 males and 4 females in the 3000 mg/kg bw d group. No other treatment-related or systemic effects were observed.	9
ORAL							
Isopropanolamine	water	Wistar rats (5/sex/group)	14 d	0, 300, 650, or 1000 mg/kg bw/d	dose-range finding study; animals treated via gavage	NOAEL - 1000 mg/kg bw/d Treatment-related effects included slightly lower food consumption in 650 and 1000 mg/kg bw/d males and females and an increased average concentration of bile acids in serum samples of 2 females from the 1000 mg/kg bw/d group (3.8 and 5.6 times that of controls).	11

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Diisopropanolamine	drinking water	Fischer 344 rats (10/sex/group)	90 d	0, 100, 500, 1000 mg/kg	OECD TG 408; rats administered test substance via drinking water; additional recovery groups from the 0 and 1000 mg/kg bw/d groups were maintained for at least 28 d post-treatment	NOAEL: 100 and 500 mg/kg bw/d for males and females, respectively Rats given 1000 mg/kg bw/d consumed less food and water and consistently weighed less than controls. Male and females that were treated with 1000 mg/kg bw/d Diisopropanolamine had increased relative kidney weights by ~ 21 and ~14%, respectively, compared to controls. without corresponding histopathological effects. Increased absolute kidney weights in 100 mg/kg males were also statistically significant, but these rats weighed more than controls and the relative kidney weights were similar to that of controls. After the recovery period, the increase in kidney weight seen in both males and females reduced by half.	[13]
Triisopropanolamine	water	female New Zealand white rabbits (3-5/group)	21 d	0 or 1000 mg/kg bw/d	dose-range finding study; animals treated via gavage	All treated animals had reduced food consumption, body weight, feces or diarrhea throughout the course of the study. Two treated rabbits died on day 3 and day 5 of treatment, respectively.	[9]
Triisopropanolamine	water and feed	Beagle dogs (4/sex/group)	102 – 104 d	500, 2000, or 7500 ppm (corresponding to mean daily intakes of 16.8 and 19.7 mg/kg bw/d, 71.2 and 78.3 mg/kg bw/d, and 272 and 288 mg/kg bw/d Triisopropanolamine for males and females, respectively)	test substance administered via feed and water	NOEL: 7500 ppm for both males and females No mortality occurred and no statistically or toxicologically significant effects were observed at any dose level	[9]

Abbreviations: NOAEL - no-observable-adverse-effect-level; NOEL - no-observed-effect-level; NR - not reported; OECD - Organisation for Economic Co-Operation and Development; TG - test guideline

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Diisopropanolamine	water	female Sprague-Dawley rats (25/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; test substance administered via gavage on GD 6-20; appropriate controls used	NOAEL for maternal and fetal toxicity: 1000 mg/kg bw/d The mean relative kidney weight of 1000 mg/kg-treated dams was 3.9% greater than control dams, which was not statistically significant. Skeletal malformations, and abnormalities of the heart and kidney occurred in the fetuses of control dams. Among the fetuses of treated dams, one fetus from the 100 mg/kg/d group had left hydroureter (enlarged and blocked ureter), one fetus from the 300 mg/kg/d group had wavy ribs of moderate to severe degree, and one fetus from the 1000 mg/kg/d group had bilateral hydroureter. Fetuses from all groups (including controls) had minor skeletal variations, most of which were delayed ossification of skull bones. There were no statistically significant differences between the incidence of fetal abnormalities in the treated groups compared to controls.	[13]
Isopropanolamine	water	Wistar rats (12/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 422; developmental and reproductive toxicity assay; administration via gavage; dosing during 2-wk premating period and continued until 2 wk post-mating for males (38 d); dosing throughout gestation and until day 4 of lactation for females (45 d)	NOAEL for maternal and developmental toxicity: 1000 mg/kg bw/d NOAEL for general systemic toxicity: 300 mg/kg bw/d (based on statistically significantly reduced hemoglobin and hematocrit values in 1000 mg/kg bw/d males, which were indicative of a mild anemic process)	[11]
Isopropanolamine	water	female Wistar rats (22/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; test substance administered via gavage on days 6 – 20 post-coitum	NOAEL for maternal and developmental toxicity: ≥ 1000 mg/kg bw/d No maternal or developmental toxicity was observed at up to the highest tested dose.	[11]
Isopropanolamine	water	Wistar rats (25 sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 443: extended one-generation reproductive toxicity assay; gavage administration; F1 males dosed for 7 d/wk for a minimum of 11 wk (prior to and during mating period); females dosed 7 d/wk for a minimum of 16 wk (at least 21 d after delivery)	NOAEL (general toxicity for F_0 and F_1): 100 mg/kg bw/d (based on histopathological findings in kidneys of males starting from 300 mg/kg/d) NOAEL (F_0 reproductive toxicity): 300 mg/kg bw/d for males and females (based on low reproductive performance in 1000 mg/kg group, (likely caused by disturbance in spermatogenesis)) NOAEL (F_1 developmental toxicity, until weaning): 300 mg/kg bw/d (based on low gestation index in 1000 mg/kg group) NOAEL (F_1 developmental toxicity, post-weaning): 1000 mg/kg bw/d (based on no adverse treatment-related effects)	[11]

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Triisopropanolamine	water	Wistar rats (25/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; test substance administered via gavage on days 6 – 15 post-coitum	NOAEL for maternal toxicity: 400 mg/kg bw/d (based on decreased weight gain and food consumption in the 1000 mg/kg group) NOEL for fetal toxicity: 1000 mg/kg bw/d (considered not determinable due to absence of adverse toxic effects) A statistically significant reduction in food consumption and body weight gain was observed in 1000 mg/kg bw/d dams, which was considered treatment related. There were no substance-related and/or biologically relevant differences between the groups in terms of conception rate, mean number of corpora lutea and implantation sites, or in the values calculated for the pre- and the post-implantation losses and the number of resorptions and viable fetuses. Any differences were considered incidental and within the normal range of deviations for animals of this strain and age. No adverse effects were observed in pups.	[9]
Triisopropanolamine	diet	rats (25/sex/group; strain not specified)	males: 0, 39.7, 160, 609 mg/kg bw/d females: 0, 43.7, 182, or 700 mg/kg bw/d	one-generation reproductive toxicity study; animals treated for 5 wk prior to mating, during mating, gestation and lactation; 20 offspring/sex/group given the same doses 90 d post-weaning	reproductive NOAEL in males: 609 mg/kg bw/d reproductive NOAEL in females: 7000 mg/kg bw/d No adverse effects observed.	[14]
Triisopropanolamine	water	Sprague-Dawley rats (25/sex/group)	0, 500, 2000, or 7500 ppm/d	one-generation reproductive toxicity study; test substance dissolved in water and administered via diet for 5 wk; parents were mated to produce offspring which were fed same diet for 90 d post-weaning	NOEL parental and fetal toxicity: 7500 ppm No differences in treated animals and controls were attributed to administration of Triisopropanolamine in gestation length, the number of litters, or any other reproductive performance parameters. No treatment-related effects were observed in the pups of the parental generation, even after being fed with Triisopropanolamine for 90 d.	[9]

GD – gestation day; NOAEL - no-observable-adverse-effect-level; NOEL – no-observed-effect-level; NR - not reported; OECD - Organisation for Economic Co-Operation and Development; TG - test guideline

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
Diisopropanolamine	water	0, 100, 333, 1000, 3333, or 10,000 µg/plate	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[10]
Diisopropanolamine	water	up to 5000 µg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[10]
Diisopropanolamine	water	up to 5000 µg/ml	Chinese hamster ovary cells	OECD TG 476; cell gene mutation assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[10]
Diisopropanolamine	cell culture medium	up to 5000 µg/ml	rat lymphocytes	chromosomal aberration assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[10]
Isopropanolamine	water	up to 5000 µg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537; *Escherichia coli* WP2	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[11]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
Isopropanolamine	water	up to 5000 μg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538; *Escherichia coli* WP2	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[11]
Isopropanolamine	water	up to 4000 μg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[11]
Isopropanolamine	water	up to 2500 μg/ml	Chinese hamster ovary cells	OECD TG 476; cell gene mutation assay (HGPRT locus) performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[11]
Isopropanolamine	water	up to 2500 μg/ml	rat lymphocytes	OECD TG 473; in vitro chromosomal aberration assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[11]
Triisopropanolamine	water	0, 100, 333, 1000, 3333, or 10,000 μg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[15]
Triisopropanolamine	water	0, 50, 167, 500, 1667, or 5000 μg/ml	Chinese hamster ovary cells	OECD TG 476; mammalian gene mutation assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[9]
Triisopropanolamine	water	0, 50, 167, 500, 1670, or 5000 μg/ml	rat lymphocytes	OECD TG 473; in vitro mammalian chromosomal aberration assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[9]
IN VIVO						
Triisopropanolamine	water	0, 500, 1000, or 2000 mg/kg bw/d	NMRI mice (5/sex/group)	OECD TG 474; mammalian erythrocyte micronucleus assay; single dose of test substance given to mice via gavage; polychromatic and nonchromatic erythrocytes in bone marrow measured 24 and 48 h after exposure; appropriate positive and negative controls used	non-genotoxic	[9]

HGPRT - hypoxanthine-guanine phosphoribosyltransferase; OECD - Organisation for Economic Co-operation and Development; TG - test guideline

Table 8. Carcinogenicity Studies

Test Article	Vehicle	Animals/Group	Procedure	Results	Reference
1% Diisopropanolamine	diet	20 male rats (strain not specified)	animals administered test substance in diet for 94 wk; control animals fed diet without test substance	no significant differences between tumor incidence in control or treated groups; 16/20 animals survived	[14]
2% Triisopropanolamine	diet	male Wistar rats (number of animals not stated)	animals administered test substance in diet for 104 wk	no histological evidence of increased liver foci observed	[14]

Table 9. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
ANIMAL						
Diisopropanolamine	none	100%: 0.5 g	6 small white Russian rabbits (sex not specified)	OECD TG 404; semi-occlusive conditions; applications for 4 h to a 6 cm^2 shaved area of the trunk	slight erythema was observed in 4/6 animals after 1 h, which was fully reversible within 48 h; Diisopropanolamine was not considered irritating	[10]
Diisopropanolamine	water	80%	2 Vienna white rabbits (sex not specified)	OECD TG 404; occlusive conditions; applications for 20 h 2.5 cm^2 area; test sites scored 24 and 48 h, and up to 8 d after application	erythema (accompanied by scale formation) seen in both animals after 20 h of exposure was reversible in 1 animal over the 8-d period; Diisopropanolamine was deemed slightly irritating.	[10]
Isopropanolamine	none	100%	6 Vienna white rabbits (sex not specified)	occlusive conditions; applications for 20 h to 2.5 cm^2 area; test sites scored 24, 48, and 72 h, and up to 8 d after application	bleeding was observed after 5 min (3/6 animals) or 15 min (4/6 animals) and scale and crust formation was observed at the end of 8 d, 1 animal after 15 min of application exhibited anemic necrosis; 20-h application led to severe edema and erythema marked by grey-blackish, relocatable necrosis beyond the application area; Isopropanolamine was classified as a Category 1B corrosive agent based on GHS criteria	[11]
Triisopropanolamine	water	15, 30, 45, 60, or 75%; 4 ml/kg	Male Fischer 344 rats (2/group)	semi-occlusive conditions; applications made to a 5 cm^2 clipped area of the back for at least 6 h/d, for 4 d; animals observed for irritation daily	very slight erythema was observed at the test site of 1 of the 2 rats that received 4 doses of 75% Triisopropanolamine	[9]
Triisopropanolamine	none	100%	6 small white Russian rabbits (3/sex)	semi-occlusive conditions; applications made to a 6 cm^2 clipped area of the back for 4 h; sites scored 24, 48, and 72 h post-application	mean erythema and edema scores and the PDII were 0 at all time points	[9]
Triisopropanolamine	NR	NR	6 Vienna white rabbits (sex not specified)	OECD TG 404; occlusive conditions; applications made to a 2.5 cm^2 area; sites scored 24, 48, and 72 h after application	no erythema or edema was observed in animals exposed for up to 15 min; all 4 animals exposed for 20 h had blotched skin after 2 – 3 d, skin and erythema which expanded beyond the application site which resolved within 6 d.for 3 animals, and persisted in 1 animal	[9]
Triisopropanolamine	water	99.6%	1 New Zealand white rabbit (sex not specified)	-10 open applications of 0.1 ml applied to the ear over 14 d, -10 semi-occlusive applications of 0.5 ml applied to intact skin to a 1 in^2 area on the shaved abdomen over 14 d -3 consecutive, semi-occlusive daily applications of 0.5 ml applied to abraded skin to a 1 in^2 area on the shaved abdomen over 3 d test sites were examined 24 h after patch removal and up to 10 d after the last application; test sites were scored on a range of 1 -6 for hyperemia, edema, necrosis, exfoliation, scab and scar formation	slight redness, very slight swelling, and very slight exfoliation and superficial burn were seen with repeated application on confined skin; after 3 applications to abraded test sites or 9 applications to intact test sites a moderate burn developed which resulted in scar formation; no other effects were noted; Triisopropanolamine was considered a possibly weak irritant.	[9]
HUMAN						
Diisopropanolamine	water	1%	61 subjects	patch test; no other details provided	no irritation observed	[10]
Diisopropanolamine	none	100%	24 subjects	patch test; no other details provided	irritation observed in 6/24 subjects	[10]

Table 9. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
SENSITIZATION						
ANIMAL						
Diisopropanolamine	distilled water	50%; 0.4 ml	male Hartley guinea pigs (10/group)	OECD TG 406; Buehler assay; occlusive applications in 25 mm patches; positive controls treated with liquid epoxy resin in di(propylene) glycol methyl ether; challenge applications applied 2 wk after induction	non-sensitizing; positive control produced expected results	[10]
Triisopropanolamine	water	22.9%; 0.1 ml	male Hartley guinea pigs (10/group)	EPA OPPTS 81-6; semi-occlusive conditions; 15 mm^2 gauze patches; induction patches made over a period of 10 d; adjuvant administered during 3rd application; challenge patches applied after 2-wk non-treatment period; positive controls treated with 10% solution of epoxy resin	non-sensitizing; positive controls produced expected results	[9]

EPA - Environmental Protection Agency; GHS - globally harmonized system; NR - not reported; OECD - Organisation for Economic Co-operation and Development; OPPTS - Office of Prevention, Pesticides, and Toxic Substances; PDII - primary dermal irritation index; TG - test guideline

Table 10. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
IN VITRO						
Diisopropanolamine	NR	100%; 0.1 ml	4 New Zealand white rabbit eyes	isolated rabbit eye test; test substance applied topically to central part of cornea for 10 s; treated eyes washed with saline, corneal opacity, thickness, and corneal swelling, and fluorescein penetration were evaluated for 4 h, after which the corneas were excised and stained to examine histopathological changes	test substance considered to be slightly irritating	[16]
ANIMAL						
Diisopropanolamine	none	100%; 0,1 ml	3 New Zealand White rabbits (sex not stated)	test substance instilled to the lower conjunctival sac of the right eye; treated eyes held shut for 1 s and rinsed with warm saline water for 10 s; reactions in the cornea, iris, and conjunctiva were scored 1, 24, 48, and 72 h after exposure	test substance considered to be slightly irritating	[16]
Diisopropanolamine	none	100%; 100 mg	6 short white Russian rabbits (sex not stated)	OECD TG 405; test substance administered for 72 h; treated eyes washed with saline and observed for up to 21 d	irreversible effects were observed in exposed eyes included heavy erythema, iritis, opacity, and chemosis; bleeding in the mucous membrane was observed in 5 animals; circum-corneal injections occurred in 4 animals after 7 d; 1 circum-corneal injection and eye reactions were not reversible within 21 d	[10]
Diisopropanolamine	none	100%; 50 µl	2 Vienna white rabbits (sex not stated)	OECD TG 405; test substance (powdered formed) applied to eyes of rabbits; eyes unrinsed and observed for up to 5 d; contralateral eyes received talcum powder (control)	fading conjunctival hemorrhage in both test eyes was not fully reversible in 1 animal; weak chemosis and erythema were also observed in talcum controls within 24 h	[10]
Isopropanolamine	none	100%; 50 µl	2 Vienna white rabbits (sex not stated)	test substance applied to eyes; eyes unrinsed and observed for up to 8 d; contralateral eyes treated with saline (control); eyes scored for chemosis, corneal opacity, conjunctival irritation, and iridial irritation at 24 and 48 h	mean scores for rabbit 1: opacity: (3/4); iritis: (2/2); erythema: (3/3) mean scores for rabbit 2: opacity: (3/4); iritis: (0/2); erythema: (3/3) Based on GHS criteria, Isopropanolamine was considered a Category 1 ocular irritant	[11]

Table 10. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
Triisopropanolamine	none	100%; 0.1 g	2 Vienna white rabbits (sex not stated)	test substance applied to eyes of rabbits; eyes washed with saline 72 h after exposure; untreated eyes served as controls; eyes scored via Draize system 1, 24, 48, and 72 h and 5, 7, 10, 12, 14, 19, and 21 d after application	severe ocular irritant corneal opacity, chemosis, and iris effects were reversible within 10 d and conjunctival irritation resolved within 12 d for 5 animals; these effects were not reversible in 1 animal after 21 d and were severe (scores up to 3 for corneal parameters)	[9]
Triisopropanolamine	none	100%; 50 µl	2 Vienna white rabbits (sex not stated)	test substance applied to eyes of rabbits; eyes unrinsed and observed for up to 8 d (readings were taken 1, 24, 48, and 72 h and 8 d after exposure); contralateral eyes served as controls	slight opacity, moderate erythema, and chemosis were observed in the eyes of both animals; although opacity persisted in 1 animal, all other symptoms resolved by the end of the 8-d observation period Category 2 eye irritant based on GHS criteria	[9]

GHS - globally harmonized system; NR - not reported; OECD - Organisation for Economic Co-operation and Development; TG - test guideline

Table 11. Occupational exposure to Isopropanolamine

Ingredient	Study Type	Study Details	Results	Reference
Isopropanolamine	multi-center patch testing	Isopropanolamine was patch-tested (as a metal-working fluid component) in 139 metalworkers at 2% in petrolatum (metalworkers occupationally exposed to metal-working fluid on consistent basis).	Four questionable reactions were observed and 1 patient tested (+), resulting in a percent positive rate of 0.7%.	[17]
Isopropanolamine	nasal provocation assay	A patient diagnosed with occupational rhinitis (alone or with asthma) was subject to a nasal provocation test using 0.5% Isopropanolamine. Response of the nasal mucosa (nasal resistance) was measured by posterior rhinomanometry. Data from the patient's medical records including occupational exposure and clinical history were also accounted for.	Isopropanolamine did not produce nasal irritation in the tested patient.	[18]
Isopropanolamine	occupational survey	The potential hazards of Isopropanolamine use in the milling department of a titanium dioxide plant were evaluated in an occupational study conducted by NIOSH.	Nine out of 15-randomly surveyed individuals in the plant reported having health issues; of these men, 5 had present dermatitis and 3 had dermatitis in the past. In 4 instances, moderate cases of definite contact dermatitis were traceable to direct contact with Isopropanolamine, or Isopropanolamine-contaminated dust. One case reported headache, epigastric pain, sore throat, and eye irritation when working around Isopropanolamine, another case mentioned a history of dermatitis related to Isopropanolamine exposure without persistent symptoms. Symptoms in 3 other cases were deemed unrelated to occupational exposure. Workers were recommended to use protective gear and employ good work practices to minimize the risk of contact dermatitis from direct Isopropanolamine exposure.	[19]

NIOSH - National Institute for Occupational Safety and Health

Table 12. Clinical studies/case reports

Ingredient	Subjects	Study Details	Reference
Diisopropanolamine	87-yr-old man	An 87-yr-old man used the same compress for lumbago for 3 wk. During the last 10 d of use, pruritic eruptions appeared on the areas the compress had been applied (bilateral lower back and upper buttock); diffuse erythema developed on the trunk and extremities. The dermatitis was treated with topical steroids. A patch test was performed with the compress ingredients and the Japanese baseline series. Positive reactions were observed on day 2 and day 4 in response to 1% Diisopropanolamine in petrolatum, fragrance mix in 8% petrolatum, and 0.05% aqueous mercuric chloride.	[20]
Diisopropanolamine	60-yr-old man	A 60-yr-old man developed erythema after applying an indomethacin ointment on his lower legs. Treatment with oral histamine and topical steroids was ineffective; treatment with oral prednisone resolved symptoms. Of the patch tested ingredients in the indomethacin ointment, positive reactions were observed in response to 1% Diisopropanolamine pet.; 11 controls had negative reactions to 1% Diisopropanolamine and 1 had a false positive reaction.	[21]
Diisopropanolamine	78-yr-old woman and 76-yr-old woman	A 78-yr-old woman presented with edematous erythema and itching on the left buttock and right knee after using a therapeutic tape to treat osteoarthritis for 1 wk. Additionally, a 76-yr-old woman developed erythema and papules on the waist after using the same therapeutic tape to alleviate lumbago for 2 wk. Positive reactions were only observed in response to Diisopropanolamine in subsequent patch tests; contact dermatitis was attributed to Diisopropanolamine exposure in both cases.	[22]
Diisopropanolamine	15-yr-old girl	A 15-yr-old girl experienced irritation on her eyelids and face for 6 mo, which was attributed to use of her personal care products. When tested with her previously used cosmetics, the subject only had a positive reaction to her eye gloss; ingredients in the eye gloss were individually patch tested in the affected individual. An undiluted, open, patch test of Diisopropanolamine produced an allergic response, which was considered more severe than just irritation, as the reaction was eczematous and spread beyond the patch test site.	[10]

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