Safety Assessment of Hydrofluorocarbon 152a as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: September 2, 2016
Panel Meeting Date: September 26-27, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer.

Cosmetic Ingredient Review
1620 L Street NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651 ◊ fax 202.331.0088 ◊
cirinfo@cir-safety.org

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: September 2, 2016
Subject: Draft Safety Assessment on Hydrofluorocarbon 152a

Enclosed is the Draft Report of the Safety Assessment of Hydrofluorocarbon 152a as Used in Cosmetics. (It is identified as *hfc152092016rep* in the pdf document).

In June 2016, CIR issued the Scientific Literature Review (SLR) for Hydrofluorocarbon 152a. This ingredient functions as a propellant in personal care products.

The Personal Care Products Council (Council) has provided an unpublished study of Hydrofluorocarbon 152a in a bovine corneal permeability study and the concentration of use surveys. Since the June announcement, the Council has provided comments on the SLR, which have been considered. The data have been incorporated into the report, and both the data and the comments can be found in this report package (*hfc152092016data1-5 and hfc152092016pcpc)*.

According to 2016 VCRP data, Hydrofluorocarbon 152a is used in 372 formulations; the majority of uses are in leave-on hair care products. The results of the concentration of use survey conducted in 2015 by the Council indicate the highest reported maximum concentration of use to be 80% in hair sprays.

In a personal communication, the Council has notified CIR staff that while Hydrofluorocarbon 152a is not restricted from use in any way under the rules governing cosmetic products in the European Union (Annex II), it may fall under a ban of domestic aerosols (personal care and household products) containing fluorinated greenhouse gasses. The Council is currently seeking information to clarify the status of the use of Hydrofluorocarbon 152a in the European Union and will report to CIR as soon as possible with their findings.

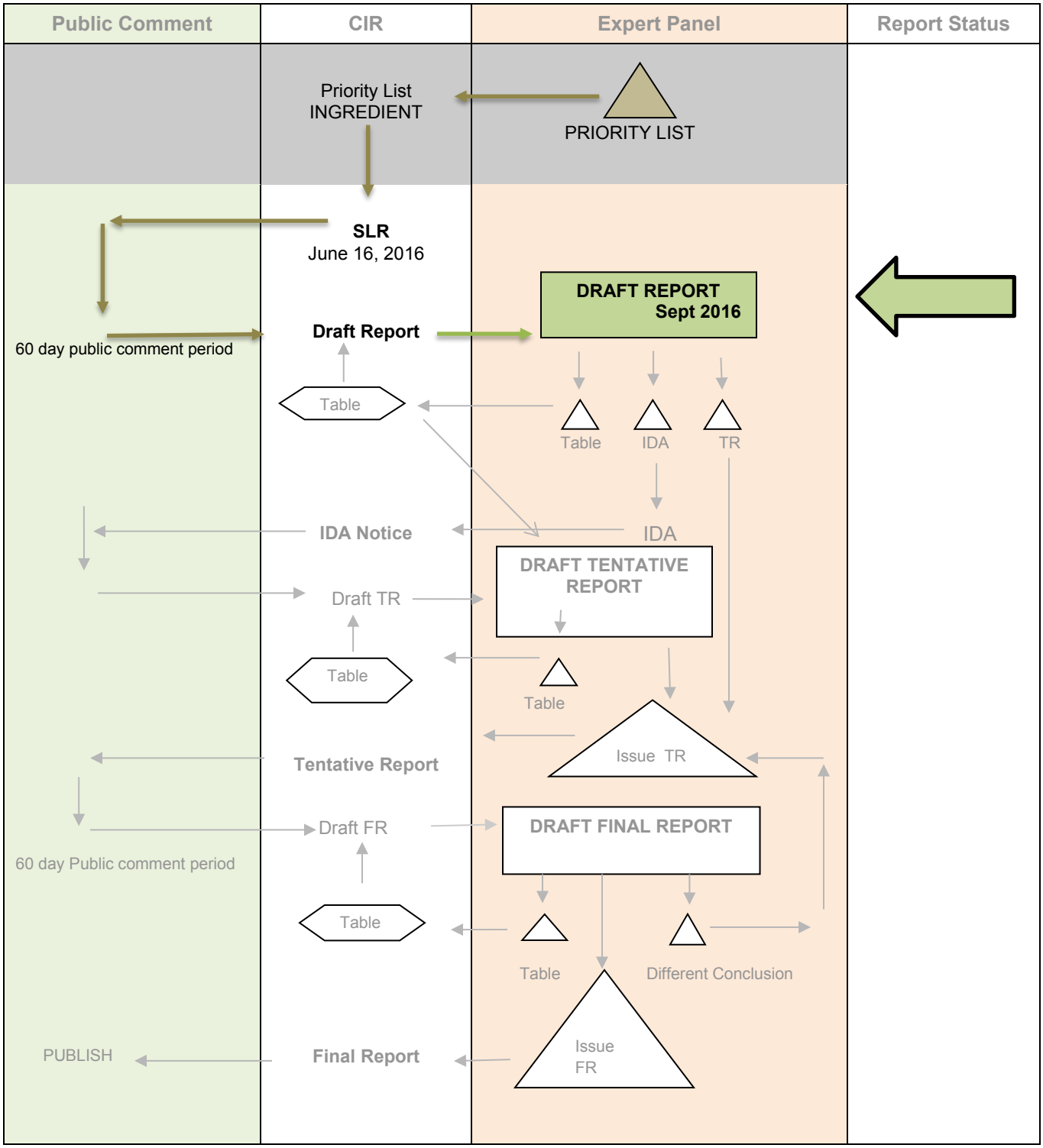
If no further data are needed, the Panel should issue a Tentative Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

1620 L St NW, Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Hydrofluorocarbon 152A

MEETING Sept 2016



Hydrofluorocarbon 152a History

June 2016 – Scientific Literature Review announced.

Hydrofluorocarbon 152a Data Profile – September 2016 – Writer, Christina Burnett														
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Toxicokinetics	Acute Toxicity	Repeated Dose Toxicity	Reproductive and Developmental Toxicity	Genotoxicity	Carcinogenicity	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
Hydrofluorocarbon 152a	X	X	X	X	X	X	X	X	X	X			X		X

"X" indicates that data were available in the category for that ingredient.

Search Strategy for Hydrofluorocarbon 152a
(Performed by Christina Burnett)

- **SciFinder – March 22, 2016**
  - CAS # search with limit to adverse events, including toxicity – 42 references

Search Terms	TOXLINE Hits (excluding PUBMED)	PUBMED Hits	SCCS/SCCP Opinion	ECHA Hits	NICNAS	OECD SIDS
hydrofluorocarbon 152a	181	2	No	No	No report	Yes -1
1,1-difluoroethane	same	58	No	Yes -1	No report	Yes (same)
75-37-6	same	25	No	Yes (same)	No report	Yes (same)

Searches conducted between March and April 2016.
Total references ordered or downloaded: 17

Search updated August 2, 2016 = 0 relevant references found.

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Cosmetic Ingredient Review

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INTRODUCTION

Hydrofluorocarbon 152a is a gas that functions as a propellant in personal care products, according to the *International Cosmetic Dictionary and Handbook*.[1] It is commonly known as 1,1-difluoroethane.

CHEMISTRY

Definition

Hydrofluorocarbon 152a (CAS No. 75-37-6) is the halocarbon, 1,1-difluoroethane, that conforms to the formula CH_3CHF_2.[1]

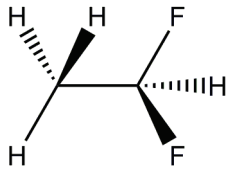

Figure 1. Hydrofluorocarbon 152a

Chemical and Physical Properties

Hydrofluorocarbon 152a is a colorless, odorless gas, with a vapor pressure of 4550 mmHg at 25 ^{o}C. This ingredient is distinct from chlorofluorocarbon propellants, such as Hydrochlorofluorocarbon 142b, because there are no chlorine atoms to react with stratospheric ozone. Physical and chemical properties of Hydrofluorocarbon 152a are provided in Table 1.

Method of Manufacturing

Hydrofluorocarbon 152a may be derived by reacting hydrogen fluoride with acetylene.[2] The material may also be produced by a catalytic reaction of vinyl chloride with hydrofluoric acid, in a closed system.[3]

Impurities

Hydrofluorocarbon 152a is reported to be greater than 99.9% pure.[3] Impurities may include water, residual hydrochloric acid, and/or residual hydrofluoric acid.

USE

Cosmetic

The safety of the cosmetic ingredient included in this assessment is evaluated based on data received from the U.S. 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 FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to the 2016 VCRP data, Hydrofluorocarbon 152a is used in 372 formulations; the majority of uses are in leave-on hair care products (Table 2).[4] The results of the concentration of use survey conducted in 2015 by the Council indicate the highest reported maximum concentration of use to be 80% in hair sprays.[5]

This product is believed to be solely used in spray products, like hair spray and spray deodorants. However, because this ingredient is a gas under all exposure conditions, inhalation is possible for all product types.

Hydrofluorocarbon 152a is not restricted from use in any way under the rules governing cosmetic products in the European Union.[6]

Non-Cosmetic

Hydrofluorocarbon 152a may be used as an aerosol propellant, a foam expansion agent, a refrigerant, and as a catalyst regenerator.[3]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Inhalation

Metabolites identified in urine collected for nuclear magnetic resonance (NMR) spectroscopy analysis from male CD rats exposed via inhalation to 3000 ppm Hydrofluorocarbon 152a (see Acute Toxicity for further study details) included fluoride ion and a trace of acetyl fluoride.[7] No fluoroacetate was detected. The time at which the urine was collected after exposure was not identified in the study report.

Human

Inhalation

The uptake, distribution, and elimination of Hydrofluorocarbon 152a were studied in male and female subjects.[8,9] Six women and 4 men completed all exposure sessions (0, 200, and 1000 ppm test material), with one additional male exposed to 0 and 200 ppm, another male exposed to only 200 ppm, and another male exposed only to 0 ppm (n for 0 ppm = 12, n for 200 ppm = 12, and n for 1000 ppm = 10). Subjects were exposed for 2 h on three separate occasions to Hydrofluorocarbon 152a vapors and exposures were performed during light exercise on computer-controlled ergometer bicycles in an exposure chamber (20 m^3) with a controlled climate. The concentration of the test material in the chamber was checked by gas chromatography (GC) at 5 minute intervals throughout the exposure sessions. Mixed exhaled air was collected once before the exposure, five times during the exposure, and seven times after the exposure. Pulmonary ventilation was recorded with an electric spirometer during every breath sampling period. Venous blood was collected from the brachial vein prior to exposure and at 3 h and 22 h after exposure for analysis of inflammatory markers, while arterialized capillary blood was collected from the subjects' finger tips before, during, and after exposure. Urine was sampled once before exposure and at 2, 4, and 6 h after onset of exposure, as well as twice in the evening and once the following morning. The existence of Hydrofluorocarbon 152a in the blood and urine was analyzed by head-space GC. The urine was analyzed for fluoride with an ion selective electrode and for potential metabolites with NMR.

In the blood, initial increases in Hydrofluorocarbon 152a were fast and average concentrations of 7.4 µM (for 200 ppm) and 34.3 µM (for 1000 ppm) were achieved within a few minutes of exposure. Within 4 h post-exposure, the concentration was less than 1% of the steady state level. Blood concentrations were below detection limits 22 h post-exposure. The area under the curve (AUC) of the test material in blood was 1042 µM at 200 ppm and 4572 µM at 1000 ppm, which indicated dose-proportional kinetics. No exposure-related effects were observed in inflammatory markers in the blood plasma. Total inhaled Hydrofluorocarbon 152a was approximately 20.6 and 99.6 mmol for the 200 and 1000 ppm exposures, respectively. Post-exposure decreases of the test material in exhaled air and urine were similar to that in blood. The AUCs of the test material in urine were 190 µM for 200 ppm and 1271 µM for 1000 ppm. After exposure to 200 ppm and 1000 ppm Hydrofluorocarbon 152a, about 0.004% and 0.009%, respectively, of the total amount inhaled was excreted in the urine within 23 h. About 20 µmol excess fluoride (0.013% of inhaled) was excreted in urine following the exposure to 1000 ppm test material when compared to the control. This was statistically significantly higher compared to both the control and the 200 ppm exposures (p=0.008) and stayed significant in the post hoc test (p<0.05). Fluoride excretion rate was varied; however, it was statistically significantly higher in the first 2 urine samples after exposure to 1000 ppm test material when compared to the control and 200 ppm exposure. (p=0.0004). No fluorine-containing metabolites could be detected in the urine, indicating biotransformation of the test material in humans was very low.[8,9]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Acute oral and inhalation studies are summarized in Table 3.[3,7,9] In rats, the lowest lethal oral dose (LD_{LO}) for Hydrofluorocarbon 152a was greater than 1500 mg/kg. The LC_{50} in a mouse inhalation study was 977,200 ppm. Cardiac arrhythmia was observed in dogs exposed for 5 min to 150,000 ppm Hydrofluorocarbon 152a in an inhalation study.

Short-Term Toxicity Studies

Inhalation

In a short-term inhalation study of Hydrofluorocarbon 152a, 10 male ChR-CD rats received 100,000 ppm of the test material for 6 h/day for 5 days/week for 2 weeks.[3,9] Following the final exposure, 5 rats were killed for gross and histopathologic examination while the remaining rats were killed after a 14-day recovery period.

Hematological, urine analytical, and biochemical indices were measured in all rats prior to being killed. During exposure to the test material, the rats appeared to be anesthetized, which was indicated by sleep and unresponsiveness to sound. No other adverse effects were observed. A slight increase in urinary fluoride was observed following the final exposure.

In another short-term study, 8 albino rats (sex not provided) were exposed to 100,000 ppm Hydrofluorocarbon 152a for 16 h/day for 2 months.[3,9] At the end of the exposure period, the animals were killed and examined for gross pathological changes. Lung and liver sections were examined microscopically. During the exposure period, no clinical signs of toxicity were observed. Necropsy indicated no adverse changes. Mild diffuse infiltration of small and large round cells in the lung was observed during microscopic examination, which indicated mild chronic irritation.

Chronic Toxicity Studies

See Carcinogenicity section below.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

The maternal and developmental toxicity of Hydrofluorocarbon 152a was investigated in mated CD rats.[3,9] Groups of 27 female rats were exposed for 6 hours/day on gestation days 6-15 via whole body inhalation to 0, 5000, or 50,000 ppm. The dams were exposed to the test material in 1.4 m^3 stainless steel and glass chambers under dynamic airflow conditions. The animals were observed daily for signs of toxicity and weighed periodically throughout the study. The dams were killed on gestation day 21, and organs of the thoracic and abdominal cavities and the fetuses were examined.

No treatment-related clinical signs of toxicity or body weight changes were observed in the dams. No statistically significant differences were observed in the numbers of corpora lutea, implantations, resorptions or live fetuses, fetal weight, or crown-rump length between the treatment groups and the controls. The pregnancy ratios at 0, 5000, and 50,000 ppm were 22/27, 21/27, and 19/27, respectively. No gross pathological abnormalities were observed in ovaries, uterine horns, vital organs, or tissues of the treated animals. External, skeletal, and internal examinations of fetuses revealed no evidence of teratogenicity. The no observed effect level (NOEL) for maternal and developmental toxicity in rats was 50,000 ppm.[3,9]

GENOTOXICITY STUDIES

In vitro and in vivo genotoxicity studies are summarized in Table 4.[3,9,10] Hydrofluorocarbon 152a was not mutagenic in Ames tests at concentrations up to 75%, but it was weakly clastogenic at 60% and 70% without metabolic activation in a chromosomal aberration test in human lymphocytes. In a rat micronucleus assay, Hydrofluorocarbon 152a was not genotoxic at concentrations up to 19,500 ppm.

CARCINOGENICITY STUDIES

In a 2-year inhalation study, male and female Crl:CD(R)Br rats were exposed to 0, 2000, 10,000, or 25,000 ppm Hydrofluorocarbon 152a for 6 h/day, 5 days/week.[3,9] There were 30 rats/sex in each exposure group, and rats were 54 days old at the first exposure. Rats were exposed whole body to the test material in chambers. Body weights were recorded twice monthly for the first 14 weeks and then once a month for the rest of the study. Animals were observed for clinical signs of toxicity twice daily during the work week while animals were observed daily for mortality on the weekends and holidays. Ten rats/sex/dose group underwent clinical pathology evaluation at 1, 3, 6, 12, 18, and 24 months, which included hematology and clinical chemistry studies. Urine was collected and analyzed the day prior to blood collection. Ten rats/sex/dose group were killed and necropsied at 3 and 12 months and all remaining surviving animals were killed and necropsied at 24 months. Gross examinations were performed on all rats and select tissues underwent microscopic examination. Organ weights were recorded and histopathological examinations were conducted on the control and high-dose groups and on any animals that died during the study. Kidney and nasal tissues at the 3 and 24 month killings were evaluated from all low- and mid-dose groups.

During the study, no statistically significant differences in body weights or body weight gains were observed. Clinical signs of toxicity observed included ocular/nasal discharge, wet/stained perinea, stained body/face, and/or swollen ears. These clinical signs were also observed in some control animals. Clinical chemistry effects included increased mean corpuscular volumes, increased serum bilirubin, increased hematocrits, and/or increased urobilinogen. Because there were no abnormalities in hematopoietic tissues or red blood cells or changes in serum bilirubin, there was no conclusive evidence of a hemolytic effect. A decrease in eosinophils and/or monocytes was observed. A dose-dependent increase was observed with urinary fluoride concentration, but there was no evidence of

fluorosis. An increase in serum creatinine and urine volume, and a decrease in urine osmolality were observed in female rats. Upon study conclusion, no treatment-related differences in organ weights were observed in male rats, but significant organ weight increases were observed in female rats at all concentrations. The biological significance of these observations in the female rats is unknown. No treatment-related tumors were observed in male and female rats. The authors of the study concluded that Hydrofluorocarbon 152a was not carcinogenic and did not produce life-shortening toxic effects in rats in this 2-year inhalation study.[3,9]

DERMAL IRRITATION AND SENSITIZATION

Dermal Irritation

No relevant published dermal irritation studies on Hydrofluorocarbon 152a were identified in a literature search for this ingredient, and no unpublished data were submitted. These studies are considered technically not feasible for gases.[9]

Dermal Sensitization

No relevant published dermal sensitization studies on Hydrofluorocarbon 152a were identified in a literature search for this ingredient, and no unpublished data were submitted. These studies are considered technically not feasible for gases.[9]

OCULAR IRRITATION STUDIES

Hydrofluorocarbon 152a at 80% in a hair spray was considered not irritating to the eye in a bovine corneal permeability (BCOP) assay.[11] The assay was performed based on methods described in Organization for Economic Co-operation and Development (OECD) test guideline 437. The test material, the positive control (ethanol), and the negative control (sterile deionized water) were applied via aerosol sprays at one second burst from a distance of 10 cm. The mean amount sprayed on each cornea was 0.9 g $\pm$ 0.19. Four to five corneas each were treated with each test article. The in vitro score was 2.3 for the test material while it was 48.4 for the positive control.

CLINICAL STUDIES

Case Reports

Numerous case reports of adverse events from abusive inhalation of products containing Hydrofluoro-carbon 152a have been described in the literature. Adverse events include death, cardiomyopathy, cardiac arrhythmia and other cardiac and respiratory effects, rhabdomyolysis, fulminant hepatitis, acute kidney injury, angioedema, frostbite, chemical burns, and even thermal burns. [12-16]

RISK ASSESSMENT

The American Industrial Hygiene Association (AIHA) 8 hour workplace environmental exposure limit for Hydrofluorocarbon 152a is 1000 ppm.[17]

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) has estimated the reference concentration for chronic inhalation exposure (RfC) for Hydrofluorocarbon 152a to be 40 mg/m^3 with an uncertainty factor of 300 and a modifying factor of 1.[18] This value was based on a no observed adverse effect level (NOAEL) value of 67,500 mg/m^3 (25,000 ppm, see Carcinogenicity section above) and adjusted for exposure scenario.

SUMMARY

Hydrofluorocarbon 152a, commonly known as 1,1-difluoroethane, is a gas that functions as a propellant in personal care products.

According to the 2016 VCRP data, Hydrofluorocarbon 152a is used in 372 formulations; the majority of uses are in leave-on hair care products. The results of the concentration of use survey conducted in 2015 by the Council indicate the highest reported maximum concentration of use to be 80% in hair sprays.

Hydrofluorocarbon 152a may be used as an aerosol propellant, a foam expansion agent, a refrigerant, and as a catalyst regenerator.

Metabolites identified in urine collected from male rats exposed via inhalation to 3000 ppm Hydrofluoro-carbon 152a included fluoride ion and a trace of acetyl fluoride.

In an uptake, distribution, and elimination inhalation study of Hydrofluorocarbon 152a in human subjects exposed to 0, 200, or 1000 ppm, initial increases of Hydrofluorocarbon 152a in the blood were fast, and within 4 h

post-exposure, the concentration was less than 1% of the steady state level. Blood concentrations were below detection limits 22 h post-exposure. Total inhaled Hydrofluorocarbon 152a was approximately 20.6 and 99.6 mmol for the 200 and 1000 ppm exposures, respectively. Post-exposure decreases of the test material in exhaled air and urine were similar to that in blood. After exposure to 200 ppm and 1000 ppm Hydrofluorocarbon 152a, about 0.004% and 0.009%, respectively, of the total amount inhaled was excreted in the urine within 23 h. Fluoride excretion rate was varied, however, it was significantly higher in the first 2 urine samples after exposure to 1000 ppm test material when compared to the control and 200 ppm exposure. No fluorine-containing metabolites could be detected in the urine, indicating biotransformation of the test material in humans was very low.

In a rat oral dose study, the LD_{Lo} for Hydrofluorocarbon 152a was greater than 1500 mg/kg. The LC_{50} of animals in a mouse inhalation study was 977,200 ppm. Cardiac arrhythmia was observed in dogs exposed for 5 min to 150,000 ppm Hydrofluorocarbon 152a in an acute inhalation study.

In a 2-week study of 100,000 ppm Hydrofluorocarbon 152a, rats appeared to be anesthetized, which was indicated by sleep and unresponsiveness to sound. No other adverse effects were observed. A slight increase in urinary fluoride was observed following the final exposure. In another short-term study, rats exposed to 100,000 ppm Hydrofluorocarbon 152a had no clinical signs of toxicity during 2 months of exposure. Necropsy indicated no adverse changes. Mild diffuse infiltration of small and large round cells in the lung was observed during microscopic examination, which indicated mild chronic irritation.

No treatment-related clinical signs of toxicity or body weight changes were observed in the dams of a maternal and developmental toxicity study of Hydrofluorocarbon 152a at concentrations up to 50,000 ppm in rats. No statistically significant differences between the control group and test groups were observed in pregnancy or fetal parameters. The NOEL for maternal and developmental toxicity in rats was 50,000 ppm.

Hydrofluorocarbon 152a was not mutagenic in Ames tests at concentrations up to 75%, but it was weakly clastogenic at 60% and 70% without metabolic activation in a chromosomal aberration test in human lymphocytes. In a rat micronucleus assay, Hydrofluorocarbon 152a was not genotoxic at concentrations up to 19,500 ppm.

The authors of a 2-year inhalation study of rats exposed to concentrations up 25,000 ppm Hydrofluorocarbon 152a concluded that this chemical was not carcinogenic and did not produce life-shortening toxic effects.

Hydrofluorocarbon 152a at 80% in a hair spray was considered not irritating to the eye in a BCOP assay.

Numerous case reports of adverse events from abusive inhalation of products containing Hydrofluorocarbon 152a have been described in the literature. Adverse events include death, cardiomyopathy, cardiac arrhythmia and other cardiac and respiratory effects, rhabdomyolysis, fulminant hepatitis, acute kidney injury, angioedema, frostbite, chemical burns, and even thermal burns.

The AIHA 8 hour workplace environmental exposure limit for Hydrofluorocarbon 152a is 1000 ppm. The EPA's IRIS has estimated the RfC for chronic inhalation exposure for Hydrofluorocarbon 152a to be 40 mg/m^3 with an uncertainty factor of 300 and a modifying factor of 1.

No relevant published dermal sensitization or dermal or ocular irritation studies on Hydrofluorocarbon 152a were identified in a literature search for this ingredient, and no unpublished data were submitted.

DISCUSSION

To be determined…

CONCLUSION

To be determined…

TABLES

Table 1. Physical and chemical properties of Hydrofluorocarbon 152a

Property	Value	Reference
Physical Form	Gas	[2]
Color	Colorless	[2]
Odor	Odorless	[2]
Molecular Weight (g/mol)	66.1	[3]
Density at -25 °C	1.004	[2]
Vapor pressure mmHg at 25 °C	4550	[3]
Henry's Law constant atm·m^3/mole	0.02	[3]
Melting Point °C	-117	[2]
Boiling Point °C	-24.7	[2]
Water solubility g/L at 25 °C	2.671 (calculated)	[3]
Log K_{ow}	0.75	[3]

Table 2. Frequency and concentration of use according to duration and type of exposure for Hydrofluorocarbon 152a[4,5]

	# of Uses	*Max Conc of Use (%)*
Totals†	**372***	**2-80**
Duration of Use		
Leave-On	364	2-80
Rinse Off	8	NR
Diluted for (Bath) Use	NR	NR
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation -Sprays	290; 42[a]	12-80; 2-45[a,b]
Incidental Inhalation - Powders	NR	NR
Dermal Contact	76	12-45
Deodorant (underarm)	18[a]	16.5-35[c]
Hair - Non-Coloring	276	2-80
Hair-Coloring	20	42.3
Nail	NR	NR
Mucous Membrane	2	NR
Baby Products	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.

* It is likely that all 372 reported uses are in spray products, but type of exposure cannot be confirmed.

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

[b.] Includes use as a hair mousse at 3-3.9%.

[c.] In spray deodorants.

Table 3. Acute studies

Concentration/Dose	Study Protocol	Results	Reference
	Oral		
200, 300, 450, 670, 1000, or 1500 mg/kg dissolved in corn oil (23 or 46 mg/ml)	Test material was dissolved in corn oil, which was then administered via gavage to 1 male Crl:CD(R)BR rat/ dose group; test material was kept under pressure in aerosol cans maintained in an ice bath; doses greater than 450 mg/kg were administered in 2 portions about 15 min apart	LD_{Lo} > 1500 mg/kg; no mortalities observed, lethargy observed at 1000 and 1500 mg/kg; high carriage, wet and yellow stained perineum , and diarrhea observed in all rats 1 to 2 days post-dosing. This study was considered invalid by OECD SIDS due to use of an unsuitable test system	3,9
	Inhalation		
896,000 to 1,065,000 ppm	Acute study in mice; exposure for 2 h (no further details provided)	LC_{50} = 977,200 ppm; narcotic effects observed at this concentration	3,9
3000 ppm	Study of several fluorinated ethanes, 3-4 CD rats exposed for 4 h in a closed, recirculating chamber; urine collected after exposure and analyzed by NMR (see Toxicokinetics-ADME section)	No adverse effects observed during or after exposure	7
66,400, 175,200, 319,000, 383,000, or 437,500 ppm	Groups of 6 male ChR-CD(R) rats exposed for 4 h in an exposure chamber	LC_{Lo} = 383,000 ppm; 1/6 rats died at 383,000 ppm; 2/6 rats died at 437,500 ppm; labored breathing, lethargy, and unresponsiveness to sound observed during exposure; no clinical signs observed after exposure nor any compound-related changes to gross pathology	3,9
100,000 to 550,000 ppm	Acute study in albino rats; exposure for 30 min (no further details provided)	No postural reflex at 200,000 ppm; no righting reflex at 250,000 ppm; no corneal reflex at 450,000 ppm; acute lung irritation $\geq$ 400,000 ppm; mortality observed at $\geq$ 500,000 ppm after 10-25 min of exposure	3,9
74,000, 100,000, or 200,000 ppm	Acute study in rats; 2 animals per concentration; whole body exposure for 2 h	Occasional trembling and incoordination during exposure; no mortalities	3,9
50,000 ppm or 150,000 ppm	Cardiac sensitization study in 12 male Beagle dogs/ group; animals exposed for 5 min via a mask on snout; animals received a 0.008 mg.kg intravenous (i.v.) injection of epinephrine before and after exposure	Cardiac arrhythmia observed in 3/12 dogs at 150,000 ppm; no response at 50,000 ppm	3,9
500,000 ppm	Acute study in 3 dogs; 2 dogs also received atropine and succinylcholine via i.v. injection (no further details provided)	Light surgical anesthesia with no change in EKG	3,9

Table 4. Genotoxicity studies

Concentration/Dose	Study Protocol	Results	Reference
	In Vitro		
0%, 20%, 30%, 40%, 50%, or 75%	Bacterial reverse mutation assay (Ames test) in *Salmonella typhimurium* strains TA97a, TA98, TA100, and TA1535 and *Escherichia coli* strain WP2uvrA (pKm101), with and without S9 metabolic activation (in accordance with OECD TG 471); plates exposed to test material in glass chambers	Not mutagenic	[3,9]
0%, 20%, 35%, or 50%	Ames test in *S. typhimurium* strains TA98, TA100, TA1535, TA 1537 with and without metabolic activation by S9; no further details provided	Not mutagenic	[3,9]
Not provided	Ames test in *E. coli* strain uvrA and *S. typhimurium* strains TA98, TA100, TA1535, TA 1537 with and without metabolic activation by S9; plates exposed to test material in gas-sampling bags	Not mutagenic	[10]
0%, 35%, 50% or 70% in 3 h exposure with and without metabolic activation; 0%, 35%, 50%, or 70% in 19 h exposure without metabolic activation; 0%, 50%, 60%, or 70% in 19 h exposure without metabolic activation	Chromosomal aberration test in human lymphocytes, with and without S9 metabolic activation (in accordance with OECD TG 473); cultures exposed to test material in gas-sampling bags	Weakly clastogenic at 60% and 70% without metabolic activation after 19 h exposure; negative with and without metabolic activation after 3 h exposure	[3,9]
	In Vivo		
0, 4875, 9750, or 19,500 ppm	Micronucleus assay in male and female Sprague-Dawley rats; animals exposed via whole body inhalation for 6 h (in accordance with OECD TG 474	No mortality or adverse clinical signs were observed during the study; no evidence of chromosome damage or bone marrow cell toxicity	[3,9]

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1. Nikitakis J and Lange B. International Cosmetic Ingredient Dictionary and Handbook. 16th *ed*. Washington, DC: Personal Care Products Council, 2016.

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2016 Raw FDA VCRP DATA

04A - Cologne and Toilet waters	75376	HYDROFLUOROCARBON 152A	7
04B - Perfumes	75376	HYDROFLUOROCARBON 152A	1
04E - Other Fragrance Preparation	75376	HYDROFLUOROCARBON 152A	46
05A - Hair Conditioner	75376	HYDROFLUOROCARBON 152A	2
05B - Hair Spray (aerosol fixatives)	75376	HYDROFLUOROCARBON 152A	216
05F - Shampoos (non-coloring)	75376	HYDROFLUOROCARBON 152A	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	75376	HYDROFLUOROCARBON 152A	42
05H - Wave Sets	75376	HYDROFLUOROCARBON 152A	2
05I - Other Hair Preparations	75376	HYDROFLUOROCARBON 152A	12
06E - Hair Color Sprays (aerosol)	75376	HYDROFLUOROCARBON 152A	20
07D - Leg and Body Paints	75376	HYDROFLUOROCARBON 152A	2
10B - Deodorants (underarm)	75376	HYDROFLUOROCARBON 152A	18
10E - Other Personal Cleanliness Products	75376	HYDROFLUOROCARBON 152A	2

Personal Care Products Council
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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 9, 2015

SUBJECT: Concentration of Use Information: Hydrofluorocarbon 152a

Concentration of Use by FDA Product Categories - Hydrofluorocarbon 152a

FDA Product Category	Maximum Concentration of Use
Colognes and toilet waters	30%
Other fragrance preparations Spray	 15-25%
Hair sprays Aerosol	 41-58.7%
Tonics, dressings and other hair grooming aids Mousse	2-45% 3-3.9%
Hair color sprays	42.3%
Deodorants Aerosol	 16.5-35%
Body and hand products Spray	 12-45%

Information collected in 2015

Table prepared October 8, 2015

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 6, 2016

SUBJECT: Updated Concentration of Use by FDA Product Category: Hydrofluorocarbon 152a

Concentration of Use by FDA Product Categories - Hydrofluorocarbon 152a

FDA Product Category	Maximum Concentration of Use
Colognes and toilet waters	30%
Other fragrance preparations Spray	 15-25%
Hair sprays Aerosol	 41-80%
Tonics, dressings and other hair grooming aids Mousse	2-45% 3-3.9%
Hair color sprays	42.3%
Deodorants Aerosol	 16.5-35%
Body and hand products Spray	 12-45%

Information collected in 2015

Table prepared October 8, 2015

Updated July 6, 2016: high concentration hair spray increased to 80%

Personal Care Products Council
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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: June 22, 2016

SUBJECT: Hydrofluorocarbon 152a

Anonymous. 2016. Summary: Bovine corneal permeability (BCOP) assay with aerosol dosing (hair spray containing 80% Hydrofluorocarbon 152a) and optional histology.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Study completed May 2016

Bovine Corneal Permeability (BCOP) assay with Aerosol Dosing and Optional Histology

Objective: The purpose of this study is to evaluate the potential ocular irritancy/toxicity of a test article as measured by the test article's ability to induce increased opacity and permeability to fluorescein. If the optional histology is needed, the potential ocular irritancy/toxicity of the test article may also be evaluated by the degree and depth of tissue injury in an isolated bovine cornea.

Test articles:

- Hairspray- test aerosol (containing 80% Hydrofluorocarbon 152a)
- Positive control: ethanol
- Negative control: sterile, deionized water

Method: The methods for the BCOP used in the study were based on the procedures described in OECD 437 (adopted 26 July 2013). Bovine corneas, obtained as a by-product from freshly slaughtered animals, were mounted in special holders and exposed to the test article. Test articles were applied to corneas as an aerosol spray (1 second burst) from a distance of 10 cm to each cornea (the mean (±SD) sprayed amount towards each cornea was 0.9 g ± 0.19). The exposure time was 10 minutes at 32 ±1°C. 4-5 corneas were treated with each test article. An in vitro score was determined for the test article based on the induction of opacity and permeability (to fluorescein) in the isolated bovine corneas.

Results: Table 1 summarizes the opacity, permeability, and *in vitro* score for the test article a n d the positive control. Since the results of the positive control fell within two standard deviations of the historical mean (within a range of 39.2 to 63.5), the assay was considered valid.

Table 1: BCOP Results of the Test Article and the Positive Control

Test Article	Conc.	Exposure Time	Opacity Value	OD_{490} Value	*In Vitro* Score	pH
Hair spray (80% HFC 152a)	Neat	10 min	2.3	0.004	2.3	5.5
Ethanol (+ control)	NA	10 min	35.3	0.870	48.4	NA

Discussion: For regulatory purposes, the in vitro score (IVIS) cut-off values for identifying test chemicals as inducing serious eye damage are found in table below:

IVIS	UN GHS
≤3	No category
>3;≤55	No prediction can be made
>55	Category 1

For non-regulatory purposes, the following classification system is established by Sina et al (*Fundamental and Applied Toxicology, 1995, 26: 20-31*) based on studies with a wide range of test materials:

IVIS	Irritation Potential
≤25	Mild Irritant
25.1-55	Moderate Irritant
>55.1	Severe Irritant

Conclusion: Based on the results of this study, the Test hair spray is considered to be nonirritating to the eye.

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 11, 2016

SUBJECT: Comments on the Scientific Literature Review Safety Assessment of Hydrofluorocarbon 152a as Used in Cosmetics (released June 16, 2016)

Key Issue

As stated in the CIR report, Hydrofluorocarbon 152a is a gas used as a propellant in cosmetic products. Therefore, if products containing this ingredient were tested in a typical HRIPT, upon application of the product to the skin, the Hydrofluorocarbon 152a in the product would enter the air and not stay on the skin. The test would only be relevant for the non-volatile ingredients in the product.

There is a REACH dossier on this ingredient on the ECHA website that is not cited in the report. Even if the studies in the dossier are duplicates of studies in the OECD SIDS report, or are considered not relevant because they are on related compounds, it would be helpful to mention in the Introduction of the CIR report that the REACH dossier exists. Also note, that under the dermal irritation and sensitization endpoints, the REACH dossier says "study technically not feasible."

Additional Considerations

Chemical and Physical Properties - If R-134a is 1,1,1,2-tetrafluoroethane, it is also a fluorocarbon not a chlorofluorocarbon as stated in the Chemical and Physical Properties section. Hydrochlorofluorocarbon 142b (1-Chloro-1,1-Difluoroethane) is an example of a chlorofluorocarbon.

ADME, Animal, Inhalation - How long after treatment was the urine collected in the rat study?

Acute, Table 3 - What were the criteria used to "select" the studies presented in the acute exposure section? If the oral study is included in the CIR report, it should be stated that the summary of this study in the SIDS dossier considered the study invalid and the test system was called unsuitable.

Carcinogenicity - It should be stated that the clinical signs observed were also observed in some of the control animals. Please state whether the changes in organ weights in female rats were increases or decreases.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Summary - Please include the route of exposure for the rat LD_{Lo}.

Table 1 - As Hydrofluorocarbon 152a is a gas, the Henry's law constant found in the SIDS dossier should be included in Table 1.

Table 3 - If the oral study is left in the report, more details about how the rats were treated orally with a gas should be included in the table. The gas in corn oil was kept in metal cylinders under pressure until just before dosing.

Table 4 - Please provide more information on how the bacteria were exposed. These were exposure of plates to atmospheres containing large concentrations of Hydrofluorocarbon 152a rather than dissolving the material in the culture media.