SUPPLEMENT

DEA Amides

Crosslinked Alkyl Acrylates

DEA

Formaldehyde

Silylates

CIR EXPERT PANEL MEETING

SEPTEMBER 26-27, 2011

DEA Amides

Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Monice M. Fiume *MMF*
Senior Scientific Analyst/Writer

Date: September 16, 2011

Subject: Wave 2 memo - Diethanolamides

Updated concentration of use data were received for the diethanolamides. The only new information is that Lauramide DEA is used in 'other shaving preparations' at 0.7%. This does not have an impact on the use tables.

These data are included with this Wave 2 memo.

1101 17th St., NW, Suite 412 Washington, DC 20036-4702
Phone 202.331.0651 FAX 202.331.0088 http://www.cir-safety.org

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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 14, 2011

SUBJECT: Updated Concentration of Use Information by FDA Product Category: Dialkanolamides

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Concentration of Use by FDA Product Category

Cocamide DEA
Almondamide DEA
Apricotamide DEA
Avocadamide DEA
Babassuamide DEA
Behenamide DEA
Capramide DEA
Cocoyl Sarcosinamide DEA
Cornamide DEA
Cornamide/Cocamide DEA
DEA-Cocoamphodipropionate
Diethanolaminooleamide DEA
Hydrogenated Tallowamide DEA
Isostearamide DEA
Lactamide DEA
Lanolinamide DEA
Lauramide DEA
Lauramide/Myristamide DEA
Lecithinamide DEA
Linoleamide DEA
Minkamide DEA
Myristamide DEA
Oleamide DEA
Palm Kernelamide DEA
Palmamide DEA
Palmitamide DEA
PEG-2 Tallowamide DEA
PEG-3 Cocamide DEA
Ricebranamide DEA
Ricinoleamide DEA
Sesamide DEA
Shea Butteramide/Castoramide DEA
Soyamide DEA
Stearamide DEA
Stearamide DEA-Distearate
Stearamidoethyl Diethanolamine
Stearamidoethyl Diethanolamine HCl
Tallamide DEA
Tallowamide DEA
Undecylenamide DEA
Wheat Germamide DEA*

Ingredient	Product Category	Concentration of Use
Cocamide DEA	Baby shampoos	2%
Cocamide DEA	Bath oils, tablets and salts	3-6%
Cocamide DEA	Other bath preparations	0.4%
Cocamide DEA	Shampoos (noncoloring)	1-7%
Cocamide DEA	Bath soaps and detergents	2-3%
Cocamide DEA	Other personal cleanliness products[1]	3%
Cocamide DEA	Shaving cream (aerosol, brushless and lather)	3%
Cocamide DEA	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	6%
Cocamide DEA	Face and neck creams, lotions and powders	1%
Cocamide DEA	Body and hand creams, lotions and powders	0.5-2%
Cocamide DEA	Paste masks and mud packs	0.5%
Lauramide DEA	Bubble baths	2-8%
Lauramide DEA	Hair sprays (aerosol fixatives)	0.3%
Lauramide DEA	Shampoos (noncoloring)	2-8%
Lauramide DEA	Tonics, dressings and other hair grooming aids	0.3-6%
Lauramide DEA	Wave sets	0.4%
Lauramide DEA	Hair tints	0.2%

Lauramide DEA	Bath soaps and detergents	4-5%
Lauramide DEA	Deodorants (underarm)	2%
Lauramide DEA	Feminine hygiene deodorants	0.2%
Lauramide DEA	Other personal cleanliness products[2]	2-4%
Lauramide DEA	Shaving cream (aerosol, brushless and lather)	1%
Lauramide DEA	Other shaving preparation	0.7%
Lauramide DEA	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	3-5%
Lauramide DEA	Foot powders and sprays	9%
Linoleamide DEA	Bubble baths	3%
Linoleamide DEA	Hair conditioners	3%
Linoleamide DEA	Shampoos (noncoloring)	7%
Linoleamide DEA	Hair dyes and colors (all types requiring caution statement and patch test)	7-12%
Linoleamide DEA	Bath soaps and detergents	7%
Linoleamide DEA	Shaving cream (aerosol brushless and lather)	1%
Myristamide DEA	Bath soaps and detergents	0.8%
Oleamide DEA	Hair dyes and colors (all types requiring caution statement and patch test)	5%
Palm Kernelamide DEA	Shampoos (noncoloring)	2%
Palm Kernelamide DEA	Other hair preparations (noncoloring)[3]	2%
Stearamide DEA	Wave sets	0.5%
Stearamidoethyl Diethanolamine	Other bath preparations	0.5%

*Ingredients found in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

[1]3% in a liquid body soap and in a shower cream

[2]2-4% in shower gel, body wash products

[3]2% in a rinse-off scalp massaging tonic

Information collected in 2011

Table prepared March 14, 2011

Updated May 16, 2011

Cocamide DEA: added low concentration Bath oils, tablets and salts; added categories: Other bath preparations and Paste masks and mudpacks; Linoleamide DEA: added high concentrations Hair dyes and colors; Oleamide DEA: added ingredient

Updated August 9, 2011 Cocamide DEA: Bath soaps and detergents: maximum concentration reduced to 3%; Lauramide DEA: Hair sprays 0.4% product removed; Bath soaps and detergents 3% product removed

Updated September 9, 2011 Lauramide DEA added other shaving preparation

Crosslinked Alkyl Acrylates

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Scientific Analyst/Writer
Date: September 16, 2011
Subject: Wave 2: Risk Assessment for Acrylates/C10-30 Alkyl Acrylates Crosspolymer

As promised in the transmittal memo for the supplement to the Crosslinked Alkyl Acrylates report, the CIR has analyzed the "benzene impurity in Acrylates/C10-30 Acrylate Crosspolymer risk assessment" that was received from the CIR Science and Support (SSC) on August 19. (This supplement should have been included in your Panel book, and is also being included with this submission.)

The document that follows presents the CIR SSC interpretation of the risk assessment findings, as well as an interpretation by Dr. Boyer.

Additionally, it was promised that the CIR would research existing safety assessments to find those that have addressed benzene. In addition to the Carbomers, which is referenced in the CIR SSC memo, only Toluene (JACT 6(1) 1987) discussed limits for benzene, stating in the Discussion that cosmetic products formulated with toluene should be benzene-free.

The other mentions of benzene in CIR safety assessments are in the 'Method of Manufacture' section of three reports. Maleic acid is manufactured by the oxidation of benzene. Hydroquinone is produced by alkylation of benzene and propylene to produce a mixture of di-isopropylbenzene isomers, followed by the isolation of the p-isomer which is oxidized with oxygen to produce the corresponding dihydroperoxide and then treated with acid to produce acetone and hydroquinone. Pyrocatechol is manufactured by the oxidation of benzene with hydrogen peroxide. There is no other discussion of benzene in those reports.

The CIR write-up and analysis of the CIR SSC data, updated concentration of use tables, the memo from the CIR SSC, and Dr. Boyer's risk assessment follow.

1101 17th St., NW, Suite 412 Washington, DC 20036-4702
Phone 202.331.0651 FAX 202.331.0088 http://www.cir-safety.org

RISK ASSESSMENT

BENZENE IN ACRYLATES/C10-30 ALKYL ACRYLATES CROSSPOLYMER

At the June 2011 meeting, the Expert Panel determined that the data were insufficient for the Panel to conclude that Acrylates/C10-30 Alkyl Acrylates Crosspolymer polymerized in benzene would be safe for use in cosmetics, and the need for a risk assessment before a safe level could be determined was discussed.

In response, the CIR Science and Support Committee (SSC) submitted an example risk assessment of Acrylates/C10-30 Alkyl Acrylates Crosspolymer polymerized in benzene as used in cosmetics.[1] Additionally, updated concentration of use data were submitted. These data indicate that the highest leave-on concentration of use of Acrylates/C10-30 Alkyl Acrylates Crosspolymer, polymerized in benzene, is 0.4%. Therefore, this is the concentration used to estimate exposure. The SSC assumed 0.41% as the concentration of benzene in raw materials, because this was the highest concentration of benzene measured in 40 batches of Acrylates/C10-30 Alkyl Acrylates Crosspolymer. (However, according to a product specification sheet, Acrylates/C10-30 Alkyl Acrylate Crosspolymer can contain 0.5% max. residual benzene.) The SSC also used 7.63 g as the 50^{the} percentile amount of body lotion applied per day and 16.83 g as the 95^{th} percentile amount applied per day, per Loretz et al. (2005).[2] Additionally, based on a discussion with Dr. Robert Bronaugh, an estimated dermal penetration factor of 10% was assumed. Although it has been shown that approximately 0.2% of 400 to 500 µl neat benzene applied to skin absorbs, with most of the applied dose evaporating within 30 seconds,[3] the potential for dermal penetration of benzene may increase when in a cosmetic product due to decreased evaporation from the skin and a corresponding increase in the duration of skin contact.

The SSC then compared the estimated exposure to benzene from Acrylates/C10-30 Alkyl Acrylates Crosspolymer as used in lotion to the daily exposure range corresponding to the Environmental Protection Agency (EPA) concentrations representing a 10^{-6} risk for cancer from benzene in drinking water.[4] The SSC stated that the estimated exposure from the use of a leave-on body product at the 50^{th} percentile, using the assumptions outlined above, are within the EPA 10^{-6} risk level, and that use at the 95^{th} percentile is just above the 10^{-6} level. According to calculations by Dr. Boyer, the 50^{th} percentile exposure estimate is within the EPA drinking water exposure range representing a 10^{-6} risk, but the 95^{th} percentile exposure estimate exceeds this range by about 38%.

The SSC then added another assumption based on their thoughts that "significant volatilization of benzene" would occur during the manufacture of the finished product, i.e., the lotion. For their calculations, the SSC assumed 10% volatilization of the residual benzene during the manufacturing process. Using this assumption, the SSC stated that exposure to the body lotion at the 95^{th} percentile is within the EPA 10^{-6} risk level. According to Dr. Boyer's calculations, with 10% of the benzene volatilized, the daily exposure range representing 10^{-6} risk is still exceeded by 24% at the 95^{th} percentile exposure level.

The CIR reviewed the assumptions put forth by the SSC, and performed its own risk assessment. During internal CIR discussions of the SSC risk assessment, Dr. Heldreth noted that he did not think it could be predicted with certainty what quantity of benzene would be volatilized/leached from Acrylates/C10-30 Alkyl Acrylates Crosspolymer during manufacture, formulation, or product use. While some benzene is inevitably volatilized during manufacture, some benzene may be trapped in the polymer matrix and may leach out during formulation and use, but there was no way of knowing how much (or if *any*) benzene would leach out without appropriate data from a representative product formulation. Dr. Boyer was concerned that more reliable values were not available to estimate the amount of benzene volatilized from Acrylates/C10-30 Alkyl Acrylates Crosspolymer during the manufacture of a finished product or for the absorption of benzene from a finished product containing Acrylates/C10-30 Alkyl Acrylates Crosspolymer. Dr. Boyer performed his own risk assessment calculations using the SSC assumptions and the two EPA slope factors for benzene, assuming a 70 kg person and life-long daily exposure.

Using the two EPA slope factors, the risk estimates for the 95th percentile usage of body lotion, assuming 10% volatilization and 10% skin absorption, ranged from 5.3 x 10^{-6} to 2.0 x 10^{-5}. For 50th percentile usage and these same assumptions, the risk estimates ranged from 2.4 x 10^{-6} to 8.9 x 10^{-6}.

Dr. Boyer then examined the effect of assuming 0% volatilized benzene on the risk estimates, still assuming 10% penetration of benzene through the skin. With no benzene volatilized during product manufacturing or use, the risk estimates ranged from 5.9 x 10^{-6} to 2.2 x 10^{-5} for 95th percentile exposure and from 2.7 x 10^{-6} to 9.8 x 10^{-6} for 50th percentile exposure.

Additionally, since the supplier specification sheet states that up to 0.5% residual benzene can exist in Acrylates/ C10-30 Alkyl Acrylates Crosspolymer, the risk assessment calculations were performed assuming 0.5% residual benzene in the raw material, as opposed to 0.41% residual benzene. With 10% benzene assumed to be volatilized during the manufacture of the finished product, the risk estimates ranged from 6.5 x 10^{-6} to 2.4 x 10^{-5} for 95th percentile exposure and from 2.9 x 10^{-6} to 1.1 x 10^{-5} for 50th percentile exposure. With no benzene volatilized, this range was 7.2 x 10^{-6} to 2.7 x 10^{-5} for 95th percentile exposure and from 3.3 x 10^{-6} to 1.2 x 10^{-5} for 50th percentile exposure.

All of these risk estimates are greater than 10^{-6}. Further calculations by Dr. Boyer determined that to get to a risk estimate of 10^{-6} at the 95th percentile exposure level, assuming 10% percutaneous absorption and 0.41% residual benzene, using the highest cancer slope factor, about 95% of the benzene would need to evaporate during the manufacturing process; with the lowest slope factor, the evaporation of benzene would need to be about 83%. For the 50th percentile exposure level, with all other assumptions as just described, about 89% of the benzene would need to evaporate for a 10^{-6} risk estimate using the highest EPA slope factor, and about 63% evaporation would be needed using the lowest slope factor.

1. Personal Care Products Council. 2011. Benzene Impurity in Acrylates/C10-30 Alkyl Acrylates Crosspolymer: Risk Assessment and Updated Concentration of Use Table. 21 pages.

2. Loretz LJ, Api AM, Barra j LM, and et al. Exposure data for cosmetic products: lipstick, body lotion, and face cream. *Food Chem Toxicol*. 2005;43:279-291.

3. Franz TJ. Percutaneous absorption of benzene. Chapter: 5. MacFarland HN, Holdsworth CE, MacGregor JA, Call RW, and Lane ML.In: *Advances in Modern Environmental Toxicology. Volume VI. Applied Toxicology of Petroleum Hydrocarbons*. Princeton, NJ: Princeton Scientific Publishers, Inc; 1984:61-70.

4. Environmental Protection Agency (EPA). IRIS summary for benzene. Last revised 1/19/2000. http://www.epa.gov/iris/subst/0276.htm. 2002.

Table 4a. **Frequency and concentration of use according to duration and type of exposure**

	# of Uses[28]	*Conc of Use (%) -**not** polymerized in benzene*	*Conc of Use (%) - polymerized **in benzene***[30]	*# of Uses*[28]	*Conc of Use (%)*[29]
	Acrylates/C10-30 Alkyl Acrylate Crosspolymer			**Acrylates Crosspolymer**	
Totals*	**1696**	**0.0002-5**	**0.05-1.1**	**2**	**0.1-4**
Duration of Use				*2*	*0.1-4*
Leave-On	*1365*	*0.0002-5*	*0.05-0.4*	*NR*	*0.3-0.8*
Rinse Off	*313*	*0.002-5*	*0.2-1.1*	*NR*	*NR*
Diluted for (Bath) Use	*18*	*1*	*NR*		
Exposure Type				NR	0.8
Eye Area	132	0.003-2	NR	NR	4
Incidental Ingestion	3	0.5	NR	NR	NR
Incidental Inhalation-Sprays	70[a,b]	0.03-2	NR	NR	2
Incidental Inhalation-Powders	6	0.0002-0.1	NR	2	0.1-4
Dermal Contact	1591	0.0002-5	0.05-1.1	NR	NR
Deodorant (underarm)	1	0.001	NR	NR	NR
Hair - Non-Coloring	77	0.1-2	0.2	NR	NR
Hair-Coloring	11	0.4-5	NR	NR	NR
Nail	9	0.1-1	NR	NR	4
Mucous Membrane	111	0.002-3	NR	NR	NR
Baby Products	10	0.2	NR		

	Acrylates/Ethylhexyl Acrylate Crosspolymer		**Acrylates/Steareth-20 Methacrylate Crosspolymer**		**Acrylates/Vinyl Isodecanoate Crosspolymer**	
Totals*	**NR**	**4-6**	**NR**	**0.1-2**	**33**	**0.2-0.5**
Duration of Use						
Leave-On	*NR*	*4-6*	*NR*	*0.1-2*	*25*	*0.3-0.5*
Rinse Off	*NR*	*NR*	*NR*	*1*	*8*	*0.2-0.5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	6	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Sprays	NR	NR	NR	NR	NR	0.4
Incidental Inhalation-Powders	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	4-6	NR	0.1-1	33	0.2-0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	2	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	1	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Acrylates/Vinyl Neodecanoate Crosspolymer		**Allyl Methacrylates Crosspolymer**		**Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer**	
Totals*	**10**	**2**	**48**	**0.003-2**	**63**	**0.06-3**
Duration of Use						
Leave-On	*4*	*NR*	*44*	*0.003-2*	*56*	*0.06-3*
Rinse Off	*4*	*2*	*4*	*0.1*	*7*	*0.2-3*
Diluted for (Bath) Use	*2*	*2*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	4	0.003-0.8	9	0.1-3
Incidental Ingestion	NR	NR	16	0.04-0.2	8	0.06-2
Incidental Inhalation-Sprays	NR	NR	2[b]	NR	1[a]	0.3
Incidental Inhalation-Powders	NR	NR	2	0.3-0.8	8	0.1-1
Dermal Contact	10	2	31	0.003-2	53	0.06-3
Deodorant (underarm)	NR	NR	NR	NR	1	0.3
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	1	NR
Mucous Membrane	6	2	16	0.04-0.2	8	0.06-2
Baby Products	NR	NR	NR	NR	NR	NR

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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: August 19, 2011

SUBJECT: Benzene Impurity in Acrylates/C10-30 Alkyl Acrylates Crosspolymer: Risk Assessment and Updated Concentration of Use Table

Benzene as a residual solvent is an issue the CIR Expert Panel has previously addressed in the Carbomer report, as a number of Carbomer ingredients are also polymerized in benzene. In the original CIR report on Carbomer (published in 1982) the following is stated in the method of manufacturing and impurities section: "The Panel calls attention to the presence of benzene as an impurity in Carbomers and recommends that every effort be made to reduce it to the lowest possible value. Benzene is a known toxic agent and human epidemiological evidence strongly suggests that it is a leukemogenic agent as well." In the re-review of Carbomers (published in 2003), it states: "The Panel acknowledged the industry practice of removing benzene from Carbomers. Resulting levels should be below those shown to have no risk to human health. For example, the Environmental Protection Agency (EPA) has established for drinking water that the 10^{-6} risk level for cancer is between 1 and 10 μg/L (EPA 2002)."

The CIR Science and Support Committee recommends that the approach used to address benzene in the CIR Carbomer report also be used in the report on the crosslinked alkyl acrylates.

In addition to use in cosmetic products, Carbomers polymerized in benzene are included in the National Formulary (NF) and have a history of use in drug products. For example, Carbomers are reported to be used in drugs in FDA's Inactive Ingredients database. The NF benzene limits for Carbomers polymerized in benzene range from 0.01% to 0.5%, with the maximum Carbomer use concentration of 58% reported for a topical lotion in a drug in the FDA's Inactive Ingredients database. Carbomer 1342, defined by NF as a "high molecular weight polymer of acrylic acid and long chain alkyl methacrylate cross-lined with allyl ethers of pentaerythritol" is similar to Acrylates/C10-30 Alkyl Acrylate Crosspolymer, defined as "a copolymer of C10-30 alkyl acrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with an allyl ether of sucrose or an allyl ether of pentaerythritol". The NF limit for benzene in Carbomer 1342 is 0.2%, with a maximum use of 0.3% reported in a topical emulsion.

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Example of a Product Specific Risk Assessment

Among the ingredients included in the CIR report on Crosslinked Alkyl Acrylates only one trade name material under the INCI name Acrylates/C10-30 Alkyl Acrylate Crosspolymer is reported to be polymerized in benzene (Carbopol 1342). Companies indicating use of Acrylates/C10-30 Alkyl Acrylate Crosspolymer were asked if they were using the ingredient polymerized in benzene. The attached concentration of use table has been updated to reflect use of Acrylates/C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene compared to the ingredient polymerized in other solvents.

The highest use concentration of Acrylates/C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene in a leave-on product was 0.4% in body product. The 50th percentile amount of body lotion applied per day was found to be 7.63 g and the 95th percentile was found to be 16.83 g (Loretz et al. 2005).

Analysis of 40 batches of the Acrylates/C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene indicated a maximum benzene level of 0.41% (from the supplier as cited in the CIR report).

A dermal penetration study of neat benzene *in vivo* (rhesus monkeys (n = 3), mini pig (n = 1), humans (n = 4)) and *in vitro* (pig-tailed macaque, mini-pig, human) indicated that benzene volatilized more rapidly than it was absorbed through the skin (Franz, 1984 [study attached]). These studies indicated that approximately 0.2% of neat benzene applied to the skin was absorbed. Application of a small amount of benzene in a cosmetic product will reduce the rate of volatilization of benzene, and thus increase the potential for dermal penetration. In a discussion with Dr. Robert Bronaugh, he agreed that a dermal penetration factor of 10% would be a reasonable estimate of dermal penetration of a volatile material such as benzene from a cosmetic product.

Estimated Exposure

0.41% benzene in raw material x 0.4% Acrylates C10-30 Alkyl Acrylate Crosspolymer in a body product
=0.00164% benzene in the product (the actual level may be lower as benzene is likely to evaporate during mixing that occurs when the product is manufactured)

50th 7.63 g body product used/day x 0.00164%
= 0.000125 g/day
= 125 µg/day

absorb 10% x 125 µg/day
= 12.5 µg/day

95th 16.83 g body product used/day x 0.00164%
= 0.000276 g/day
= 276 µg/day

absorb 10% x 276 µg/day
= 27.6 µg/day

Comparison to Risk Level

The Environmental Protection Agency (EPA) 10^{-6} risk level for cancer is between 1 and 10 µg/L in drinking water (EPA 2002). Assuming a consumption of 2 L of water each day this results in a value of 2 to 20 µg/day. The estimated exposure from the use of a leave-on body product at the 50th percentile, containing the greatest concentration of C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene is in within the range of the EPA 10^{-6} risk level, while use at the 95th percentile is just above the EPA 10^{-6} risk level. At this point it is important to note that significant volatilization of benzene would occur during the manufacture of the finished product as the temperatures reached during processing are at or near the boiling point of benzene (80.1 °C). Assuming only 10% of the residual benzene is volatilized during product manufacture, would yield an exposure within the EPA 10^{-6} risk level for use of a body lotion at the 95th percentile.

References

EPA. 2002. IRIS Summary for benzene. Last revised 1/19/2000. http://www.epa.gov/iris/subst/0276.htm .

FDA Inactive Ingredient Database. 2011. http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Accessed August 4, 2011.

Franz TJ. 1984. Percutaneous absorption of benzene. In: MacFarland HN, Holdsworth CE, MacGregor JA et al., eds. Advances in modern environmental toxicology. Vol. VI. Applied toxicology of petroleum hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, Inc., 61-70. [attached]

Loretz LJ, Api AM, Barraj LM, et al. 2005. Exposure data for cosmetic products: lipstick, body lotion, and face cream. Food and Chemical Toxicology 43: 279-291.

The United States Pharmacopeial Convention (USP). 2008. The United States Pharmacopeaia 32/The National Formulary 27. The United States Pharmocopeial Convention, Rockville MD.

Concentration of Use by FDA Product Category*

Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Acrylates Crosspolymer
Acrylates/Ethylhexyl Acrylate Crosspolymer
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer
Acrylates/PEG-4 Dimethacrylate Crosspolymer
Acrylates/Steareth-20 Methacrylate Crosspolymer
Acrylates/Vinyl Isodecanoate Crosspolymer
Acrylates/Vinyl Neodecanoate Crosspolymer
Allyl Methacrylate/Glycol Dimethacrylate Crossolymer
Allyl Methacrylates Crosspolymer
Butyl Acrylate/Glycol Dimethacrylate Crosspolymer
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer
Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer
Acrylates/C12-13 Alkyl Methacrylates/Methoxyethyl Acrylate Crosspolymer
Methacrylic Acid/PEG-6 Methacrylate Crosspolymer
PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer
Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates Crosspolymer-2
Sodium Acrylates/Vinyl Isodecanoate Crosspolymer
Stearyl/Lauryl Methacrylate Crosspolymer

Ingredient	**Product Category**	**Concentration of Use**
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (polymerized in benzene)	Shampoos (noncoloring)	0.2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (polymerized in benzene)	Skin cleansing (cold creams, cleansing lotions, liquids and pads)[1]	0.2-1.1%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (polymerized in benzene)	Face and neck creams, lotions and powders	0.05%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (polymerized in benzene)	Body and hand creams, lotions and powders	0.08-0.4%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (polymerized in benzene)	Moisturizing creams, lotions and powders	0.3%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (polymerized in benzene)	Suntan gels, creams and liquids	0.3%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Baby lotions, oils, powder and creams	0.2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Bath oils, tablets and salts	1%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Bubble baths	1%

Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Other bath preparations	1%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Eyeliner	0.03-0.4%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Eye shadow	0.05-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Eye lotion	0.2-0.6%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Eye makeup remover	0.1-0.6%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Mascara	0.003%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Colognes and toilet waters	0.03-0.2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Perfumes	0.3%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Powders (dusting and talcum)	0.1%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Other fragrance preparations	0.2-0.7%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Hair conditioners	0.1-0.4%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Hair sprays (aerosol fixatives)	2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Shampoos (noncoloring)	0.5-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Tonics, dressings and other hair grooming aids	0.2-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Other hair preparations (noncoloring)	0.6%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Hair dyes and colors (all types requiring caution statement and patch test)	0.4%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Hair color sprays (aerosol)	2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Hair bleaches	5%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer	Other hair coloring preparations	0.6%

(not polymerized in benzene)		
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Blushers (all types)	3%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Face powders	0.0002%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Foundations	0.03-0.3%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Lipstick	0.5%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Makeup bases	0.1-0.3%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Cuticle softeners	1-5%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Nail creams and lotions	0.1-0.8%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Nail polish and enamel	1%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Bath soaps and detergents	0.002-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Deodorants (underarm)	0.001%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Other personal cleanliness products	2-3%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Aftershave lotions	0.2-0.8%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Shaving cream (aerosol, brushless and lather)	1-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Other shaving preparations	0.9%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.2-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Face and neck creams, lotions and powders	0.1-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Body and hand creams, lotions and powders	0.2-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Body and hand sprays	0.2-0.5%

Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Moisturizing creams, lotions and powders	0.2-1%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Night creams, lotions and powders	0.1-2%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Paste masks (mud packs)	0.1-1%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Skin fresheners	0.7%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Other skin care preparations[2]	0.2-0.8%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Suntan gels, creams and liquids	0.2-0.5%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Indoor tanning preparations	0.1-0.6%
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (not polymerized in benzene)	Other suntan preparations	0.4-0.5%
Acrylates Crosspolymer	Eye lotion	0.8%
Acrylates Crosspolymer	Face powders	2%
Acrylates Crosspolymer	Foundations	0.1-0.6%
Acrylates Crosspolymer	Lipstick	4%
Acrylates Crosspolymer	Makeup bases	0.5%
Acrylates Crosspolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.8%
Acrylates Crosspolymer	Face and neck creams, lotions and powders	0.3-0.5%
Acrylates Crosspolymer	Night creams, lotions and powders	0.3%
Acrylates Crosspolymer	Paste masks (mud packs)	0.3%
Acrylates/Ethylhexyl Acrylate Crosspolymer	Eye shadow	6%
Acrylates/Ethylhexyl Acrylate Crosspolymer	Foundations	5%
Acrylates/Ethylhexyl Acrylate Crosspolymer	Other makeup preparations	4%
Acrylates/Steareth-20 Methacrylate Crosspolymer	Tonics, dressings and other hair grooming aids	2%
Acrylates/Steareth-20 Methacrylate Crosspolymer	Bath soaps and detergents	1%
Acrylates/Steareth-20 Methacrylate	Face and neck creams, lotions and	0.1%

Crosspolymer	powders	
Acrylates/Vinyl Isodecanoate Crosspolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.2-0.5%
Acrylates/Vinyl Isodecanoate Crosspolymer	Face and neck creams, lotions and powders	0.5%
Acrylates/Vinyl Isodecanoate Crosspolymer	Body and hand creams, lotions and powders	0.4%
Acrylates/Vinyl Isodecanoate Crosspolymer	Night creams, lotions and powders	0.3%
Acrylates/Vinyl Isodecanoate Crosspolymer	Suntan gels, creams and liquids	0.4%
Acrylates/Vinyl Isodecanoate Crosspolymer	Other suntan preparations	0.4%
Acrylates/Vinyl Neodecanoate Crosspolymer	Bubble baths	2%
Acrylates/Vinyl Neodecanoate Crosspolymer	Other personal cleanliness products	2%
Allyl Methacrylates Crosspolymer	Eye shadow	0.003-0.2%
Allyl Methacrylates Crosspolymer	Eye lotion	0.8%
Allyl Methacrylates Crosspolymer	Mascara	0.2%
Allyl Methacrylates Crosspolymer	Face powders	0.3-0.8%
Allyl Methacrylates Crosspolymer	Foundations	0.3-2%
Allyl Methacrylates Crosspolymer	Lipstick	0.04-0.2%
Allyl Methacrylates Crosspolymer	Other makeup preparations	0.07%
Allyl Methacrylates Crosspolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.1%
Allyl Methacrylates Crosspolymer	Face and neck creams, lotions and powders	2%
Allyl Methacrylates Crosspolymer	Night creams, lotions and powders	0.2%
Allyl Methacrylates Crosspolymer	Skin fresheners	1%
Allyl Methacrylates Crosspolymer	Other skin care preparations	0.2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Eyeliner	0.2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Eye shadow	0.1-3%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Blushers (all types)	0.2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Face powders	0.1-1%

Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Foundations	0.1-2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Lipstick	0.06-2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Other makeup preparations	0.7-2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Deodorants (underarm)	0.3%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.4-3%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Depilatories	0.2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Face and neck creams, lotions and powders	0.2-1%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Body and hand creams, lotions and pwoders	2%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Paste masks (mud packs)	1%
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	Other skin care preparations	3%
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.004-0.1%
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer	Face and neck creams, lotions and powders	0.1-4%
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Eye shadow	0.009%
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Blushers (all types)	1%
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Face powders	1%
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Foundations	0.3-0.4%
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Lipstick	0.4%
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Makeup bases	0.3%
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Other makeup preparations	1%

Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	Face and neck creams, lotions and powders	0.5%
Sodium Acrylates Crosspolymer-2	Body and hand creams, lotions and powders	0.8%

*Ingredients found in the title but not found in the table were included in the concentration of use survey, but no uses were reported.

[1]1.1% in a body wash

[2]0.6%, 0.8% in rinse-off skin care products

Information collected in 2010

Table prepared January 5, 2011

Table updated January 28, 2011 (Acrylates/C10-30 Alkyl Acrylate Crosspolymer: lowered low concentration Indoor tanning preparations, added low concentration Other suntan preparations; Acrylates/Vinyl Isodecanoate Crosspolymer:added Other suntan preparations)

Table updated August 18, 2011 (differentiated between Acrylates/C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene, and not polymerized in benzene)

Advances in Modern
Environmental Toxicology

VOLUME VI

APPLIED TOXICOLOGY OF PETROLEUM HYDROCARBONS

Editors:

H. N. MacFARLAND
C. E. HOLDSWORTH
J. A. MacGREGOR
R. W. CALL
M. L. LANE

Published by:

PRINCETON SCIENTIFIC PUBLISHERS, INC.
Princeton, New Jersey 08540

CHAPTER 5

PERCUTANEOUS ABSORPTION OF BENZENE

Thomas J. Franz
Dermatopharmacology Laboratory
University of Washington
Seattle, Washington

ABSTRACT

A critical factor in the evaluation of the risk associated with cutaneous exposure to toxic substances is information relating to the percutaneous absorption of those substances. Widespread exposure to benzene in the industrial environment and knowledge of its carcinogenicity has prompted an evaluation of its absorption through the skin.

The percutaneous absorption of benzene has been measured in the monkey, the miniature pig, and man using both *in vitro* and *in vivo* techniques. Following the application of a thin layer (5-10 μl/cm²) of benzene *in vivo*, absorption was found to average less than 0.2% of the applied dose in all species studied. Under the conditions of these experiments, the remainder of the applied material quickly volatized and was lost to the atmosphere. Total absorption was 0.14% in the monkey, 0.09% in the mini-pig, and 0.05% in man. Peak excretion of radioactivity occurred in the first two hours and decreased rapidly thereafter. *In vitro* studies demonstrated rapid penetration of benzene through the skin. When the same dose applied *in vivo* was used *in vitro*, the peak rate of absorption occurred at 15-40 minutes and total absorption was similar to that measured *in vivo*. Absorption was 0.19% in the monkey, 0.23% in the mini-pig, and 0.10% in man. Benzene absorption was found to be a function of its contact time with the skin. Application of progressively larger doses which persisted on the skin for up to 3 hours resulted in 10-100 times greater absorption. Total absorption was found to be directly related to the length of time benzene remained on the skin.

It can be concluded that a major factor controlling the percutaneous absorption of benzene is its contact time with the skin. Under ideal conditions in which the contact time is short due to its inherent volatility, less than 0.2% of the applied dose will be absorbed, or approximately 0.01 μl/cm². The *in vitro* technique used in this study appears to be a valid means by which to assess the percutaneous absorption of benzene.

INTRODUCTION

There is increasing concern over the skin as a route of entry into the body for toxic substances, particularly in the work environment where the number of potentially harmful substances is large and exposure may be of long duration. Whereas the skin had previously been thought to be a relatively impervious barrier, more recent work has clearly shown that it is a barrier of variable permeability (1). Though many substances penetrate poorly, if at all, others are relatively well-absorbed. Indeed, it has been shown that the skin is quite permeable to simple organic compounds such as benzoic acid and dinitrochlorobenzene, with approximately 25%-50% of the applied dose being absorbed in 24 hours (2, 3). Thus, a critical factor in the evaluation of the risk associated with cutaneous exposure to toxic substances is information relating to their percutaneous absorption. In this study, the percutaneous absorption of benzene, a known carcinogen widely used in industry, has been measured in animals and man using both *in vitro* and *in vivo* techniques.

MATERIALS AND METHODS

Radioisotopes

All studies were conducted using ^{14}C-benzene, 40 mCi/mmole (New England Nuclear Corporation, Boston, MA). Prior to use, it was diluted with reagent-grade, unlabelled benzene (Mallinkrodt) to reduce its specific activity to a workable range.

In Vivo Experiments

Animal Studies

Three adult rhesus monkeys of each sex and one mini-pig of the improved Pitman-Moore strain (VitaVet Laboratories, Inc. Marion, IN) of each sex were used to assess benzene absorption.

The basic procedure was the same in both cases. At least 24 hours prior to an experiment, the animal's back was shaved with electric clippers; it was then placed in a metabolic chair (monkey) or cage (mini-pig) for the collection of control urine specimens. Subsequently, 0.5 ml of benzene containing 100 μCi ^{14}C-benzene was applied to the back and allowed to flow over the skin, seeking its own area. Application was made with the animal positioned in front of a fume hood so that as the material volatized, none was inhaled.

There was no way to assure that the rate of evaporation was the same for each animal under these conditions. However, in all cases, the applied dose was not visible after 30 seconds. In a separate series of experiments, the dye oil red O was incorporated into nonradioactive benzene and applied to the back, under the same experimental conditions, to allow measurement of the application area. It was found to vary from 55-75 cm^2.

All urinary excretion was collected over the next 2-4 days and analyzed for radioactive content. A 5 ml aliquot of urine was gelled by the addition of 10 ml Aquasol-2 (New England Nuclear Corporation, Boston, MA) counted in a Beckman liquid scintillation spectrometer, and corrected for quenching by the external standard method. To ensure obtaining frequent urine specimens at early times in the monkey experiments, the animals were given fruit immediately before and after benzene application. If an animal did not void within the first 90 minutes, an intramuscular injection of 1 mg/kg furosemide was given. This was not done with the mini-pigs.

In order to properly quantitate percutaneous absorption from urinary excretion data, it is necessary to know what fraction of an absorbed dose is excreted in the urine since this is only one of several possible excretory pathways available to benzene. This factor was determined in the rhesus monkey by means of a subcutaneous injection of benzene. In a separate series of experiments, approximately 0.05 ml radioactive benzene was injected into the subcutaneous space of the back. As before, the animal was confined to a metabolic chair and all urinary excretion collected and assayed for radioactive content. Special care was taken to ensure that none of the injected material leaked back through the needle track as this could result in an underestimation of the fraction excreted in the urine. Leakage was most easily detected by the positioning of a Geiger-Muller tube adjacent to the injection site. Only radioactive material which had leaked onto the surface of the skin would register on the detector, as the thickness of the skin itself was sufficient to screen out radioactivity in the subcutaneous space.

Human Studies

Four adult males in good health and without evidence of skin disease were used to measure benzene absorption. With the volunteer seated in front of a fume hood and wearing a respirator suitable for trapping organic vapors, 0.4 ml benzene containing 100 μCi ^{14}C-benzene was applied to 80 cm^2 of ventral forearm. All urine was collected and analyzed for radioactive content until background levels of activity were reached. An aliquot of each urine specimen was assayed following the same procedure used in the animal experiments. All data were corrected for incomplete urinary excretion using the factor determined from the monkey subcutaneous experiments.

In Vitro Experiments

Benzene absorption *in vitro* was measured using a previously published method which had been shown to give results correlating well with those obtained *in vivo* (3, 4). Skin from man, monkey, and mini-pig was used in these experiments so that comparison to the *in vivo* could be made. All skin was obtained at autopsy. (Human abdominal skin was obtained from local hospitals. Back skin from *Macaca memestrina* monkeys was supplied by the University of Washington Regional Primate Center (supported by Grant

#RR00166 from the National Institutes of Health), and back skin from VitaVet mini-pigs was obtained from animals sacrificed in our own laboratory.)

Essentially, the method consists of mounting freshly obtained split thickness skin between two halves of specially contructed diffusion chambers. The dermis is bathed by isotonic saline, pH 7.4, 37°C, and stirred by a teflon-covered magnet which is driven by an externally mounted 600 RPM timing motor. The epidermis is exposed to ambient laboratory conditions (21°-22°C, 35%-50% relative humidity). Following a 1-2 hour equilibration period, radioactive benzene is pipetted onto the epidermis by micropipette and the rate of absorption measured by serially sampling the dermal bathing solution. At each sampling time, the dermal bathing solution is removed in its entirety, replaced with fresh solution, and a 3 ml aliquot gelled by the addition of 4 ml Aquasol-2 and assayed by liquid scintillation counting.

RESULTS AND DISCUSSION

In Vivo Studies

Data showing the excretion of radioactivity in the urine following application of ^{14}C-benzene to the skin of man are given in Figure 1. It can be noted that in each case, the rate of excretion is greatest in the first or second collection period, occurring at 2 hours or less in three of the four volunteers, and declines rapidly thereafter. Though detectable amounts of activity are present in the urine for up to 36 hours, more than 80% of the total excretion occurs in the first 8 hours. After that time, the rate of excretion falls to very low levels which

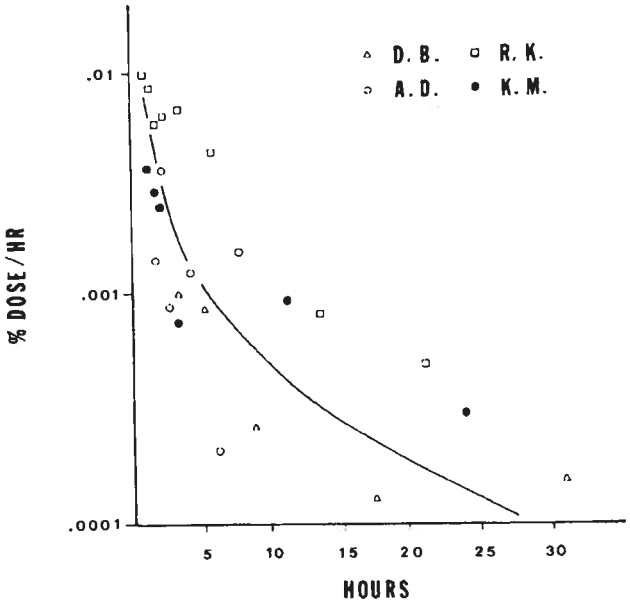

FIGURE 1. Urinary excretion of radioactivity following application of 0.4 ml ^{14}C-benzene to the ventral forearm of 4 human subjects.

are difficult to accurately measure because the amount of radioactivity present in each sample so closely approximates background. Total excretion of radioactivity in the four volunteers studied was found to be 0.023 ± 0.022% of the applied dose (Table 1).

The rate of excretion of radioactivity obtained in both the mini-pig and monkey was qualitatively similar to that seen in man. That is, the first two samples always contained the highest counts. In the mini-pig, however, the lack of an adequate number of urine specimens in the first 12 hours made meaningful comparisons of the kinetics of excretion virtually impossible. The results obtained in the rhesus monkey are given in Figure 2.

Although the overall time course of excretion is similar to that seen in man, a significant quantitative difference between the two exists. Total excretion of radioactivity was found to be three times higher in the monkey than in man with a mean value of 0.065 ± 0.037% of the applied dose. The comparable value determined in the mini-pig was 0.042% ± 0.017% (Table 1). Using the Student's *t* test, the mean urinary excretion in the monkey was found to differ significantly ($p = 0.05$) from that observed in man.

From the data on the urinary excretion of radioactivity, the percutaneous absorption of benzene can be calculated. To do this, it is necessary to know only what percentage of systemically absorbed benzene is excreted in the urine. This figure has been experimentally determined following subcutaneous injection of ^{14}C-benzene in the rhesus monkey and found to be 43.3 ± 8.9% (mean ± standard deviation of 6 animals). Therefore, the values obtained for the urinary excretion of radioactivity when multiplied by the factor to correct for excretion via other routes (100/45.3 = 2.2) give the amount of benzene absorbed through the skin following topical application. These calculated values are listed in Table 2 with the correction factor determined in the monkey used to adjust the mini-pig and human data as well.

TABLE 1. Urinary Recovery of Radioactivity Following Topical Application of ^{14}C-Benzene.

Monkey		Mini-Pig		Man	
Subject	% of dose	Subject	% of dose	Subject	% of dose
13-6, M	0.048	M-1	0.030	DB	0.008
14-6, M	0.046	F-2	0.054	AD	0.006
15-6, M	0.033			KM	0.025
X-23, F	0.076			RK	0.054
X-25, F	0.135				
X-26, F	0.052				
Mean ± SD	0.065 ± 0.037		0.042 ± 0.017		0.023 ± 0.022

It can be seen from these data that the percutaneous absorption of benzene is quite low, ranging from 0.05% of the dose in man to 0.14% of the dose in the rhesus monkey. The vast majority of the applied benzene, approximately 99.9%, apparently volatilizes to the atmosphere under the experimental conditions utilized in this study. It was noted by direct observation that liquid benzene was undetectable on the skin surface within 30 seconds of its application. Thus, because of its high volatility, a critical factor controlling the percutaneous absorption of benzene is its contact time with the skin.

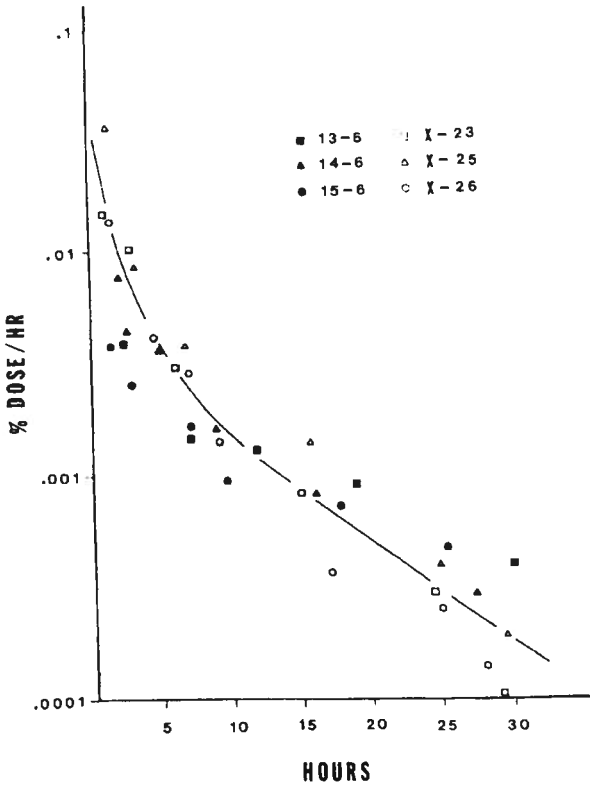

FIGURE 2. Urinary excretion of radioactivity following application of 0.5 ml ^{14}C-benzene to the shaved backs of 3 male (solid) and 3 female (open) rhesus monkeys.

TABLE 2. Benzene Absorption (% of dose[1]).

	In Vivo	Number of Experiments	*In Vitro*	Number of Experiments
Monkey	0.14 ± 0.08	6	0.19 ± 10	3
Mini-Pig	0.09 ± 0.04	2	0.23 ± 0.10	5
Man	0.05 ± 0.05	4	0.10 ± 0.004	9

[1]Dose = 5 µl/cm^2.

In Vitro Studies

In order to examine the relationship between benzene absorption and skin contact time and, also, to more closely define the kinetics of absorption, *in vitro* studies were conducted. A representative experiment is shown in Figure 3. Three pieces of skin from the same monkey were exposed to varying doses of ^{14}C-benzene, 5 μl/cm^2, 10 μl/cm^2, and 200 μl/cm^2.

Several things should be noted from this data. Diffusion of benzene through the skin is very rapid with the peak rate of absorption occurring at 15-20 minutes. The lag time is so short that within minutes, measurable radioactivity can be found in the dermal bathing solution. To date, of the limited compounds whose percutaneous absorption has been studied, no compound has been found that permeates the skin as rapidly as benzene (2, 3, 5, 6)

At the lowest dose (5 μl/cm^2) which corresponds to that used in the *in vivo* experiments, the rate of absorption rises to a maximum at approximately 20 minutes, then rapidly falls off over the next 2 hours. Though the rate of absorption is quite low after 3 hours, measurable absorption continues for at least 24 hours. This time course correlates well with that observed *in vivo* and suggests that part, if not all, of the long tail on the rate of excretion curve reflects continued percutaneous absorption of benzene rather than delayed excretion of material previously stored or bound within the body. The rate of absorption profile determined *in vitro* for both the mini-pig and man is similar to that seen in the monkey, although the maximum rate of absorption occurs somewhat later, generally 20-40 minutes.

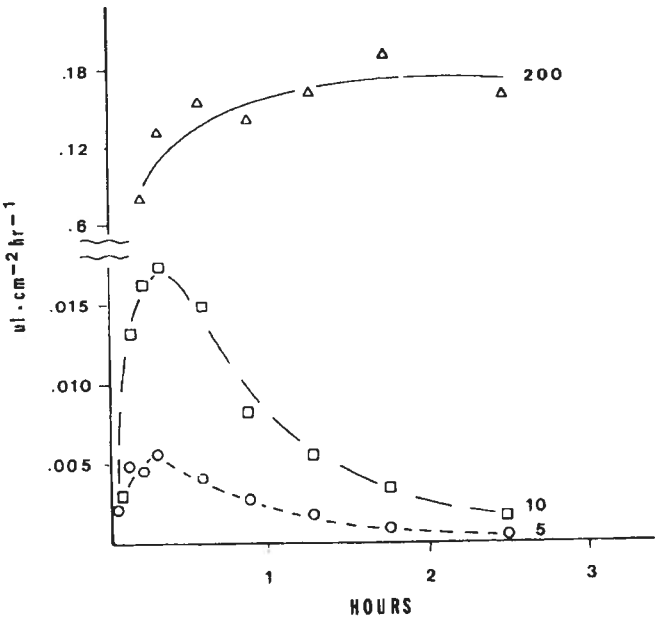

FIGURE 3. Rate of absorption of ^{14}C-benzene *in vitro* following application of 5, 10, or 200 μl/cm^2 to monkey skin.

Total absorption varies significantly among the three species studied, and the data for the 5 μl/cm² dose are given in Table 2. Percutaneous absorption of benzene is lower in man than in either the mini-pig or monkey; this is consistent with the observations made *in vivo*. Given the limited number of experiments, there is reasonable agreement between the *in vitro* and *in vivo* sets of data, and it appears as if the *in vitro* approach may offer a valid method for the quantitation of benzene absorption.

Benzene absorption increases as the size of the applied dose increases (Figure 3). From the laws of diffusion, this is to be expected. It can be seen that at the highest dose, a steady state is achieved, that is, the rate of absorption becomes constant. Failure to reach a steady state at lower doses is due to the rapid volatilization of benzene from the skin surface and, therefore, the absence of a source to continually support the absorption process. At higher doses in which a layer of liquid benzene can be maintained on the skin for several hours, the steady state is always observed. The relationship between dose and benzene absorption has been carefully evaluated in human skin and the data are given in Table 3 and plotted in Figure 4.

As can be noted from the figure, the relationship between dose and absorption appears to be linear. This is largely the result of the rapidity with which benzene diffuses through the skin and attains the steady state. Once the steady state is attained and the rate of absorption is constant, the amount of benzene absorbed can only increase in direct proportion to the length of time it remains on the skin. An exception to this is possible if benzene were capable of damaging the skin. Under those circumstances prolonged exposure could lead to increasing skin damage and result in an increasing rate of benzene absorption with time. However, the present data do not support this possibility.

Although the use of an increasing benzene dose is a convenient tool that can be used under *in vitro* conditions to study benzene absorption, it may be of limited toxicologic relevance as such. In an *in vitro* experiment, the dose/cm²

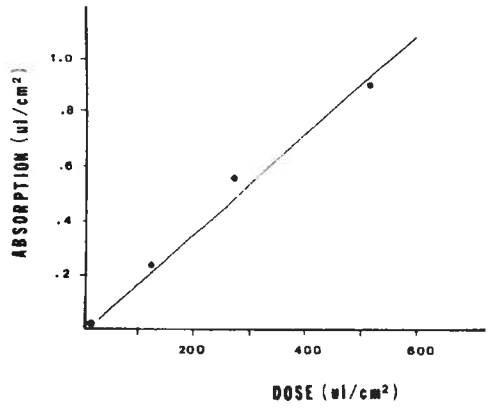

FIGURE 4. Total absorption of benzene *in vitro* in human skin following application of 5, 120, 270 or 520 μl/cm².

TABLE 3. Benzene Absorption (μl/cm²) *In Vitro*: Human Skin.

Skin	5 μl/cm²	120 μl/cm²	270 μl/cm²	520 μl/cm²
1	0.018	0.156	—	—
2	0.012	0.264	0.486	1.01
3	0.007	0.264	—	1.09
4	0.010	—	—	—
5	0.009	—	—	—
6	0.007	0.201	—	0.783
7	0.008	0.241	—	0.557
8	0.014	0.232	0.513	1.08
9	0.006	0.236	0.478	0.899
	—	0.297	0.751	—
X ± SD	0.010 ± 0.004	0.236 ± 0.043	0.557 ± 0.130	0.903 ± 0.206

can be increased readily by adding more benzene to the chamber in contact with the epidermis. This is less likely to occur in the industrial setting since, under conditions in which a worker is exposed through spill or splash, the excess would run off or be absorbed by clothing. Only in a situation where there is direct immersion of some body part in benzene would the *in vitro* conditions used here be completely relevant.

A parameter which would appear to have more utility than dose is contact or exposure time. The exposure times, *i.e.*, the time to complete evaporation, in the human *in vitro* experiments reported in Table 3 were observed and noted at each dose level. The relationship between exposure time and absorption is presented in Figure 5. It can be noted that, just as the relationship between dose

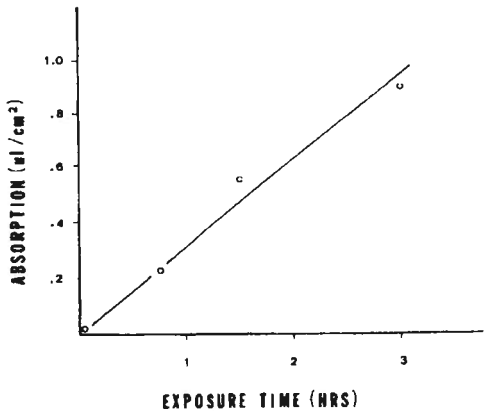

FIGURE 5. Total absorption of benzene *in vitro* in human skin as a function of the time benzene remained on the skin.

and absorption appears to be linear, the relationship between exposure time and absorption is also linear. This observation has great practical importance since it suggests that it may be possible to estimate benzene absorption in an industrial environment from knowledge of the area of skin exposed and the exposure time.

Further work is needed to substantiate this relationship and also to define the role of the vehicle (solvents or mixtures other than pure benzene) in controlling the percutaneous absorption of benzene.

ACKNOWLEDGMENT

The technical assistance of Paul Lehman is gratefully acknowledged.

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Risk Assessment Estimates, based on the CIR Science and Support Committee (SSC) Example (see: "Benzene Impurity in Acrylates/C10-30 Alkyl Acrylates Crosspolymer: Risk Assessment and Updated Concentration of Use Table," Memo from CIR SSC to Dr. F. Alan Andersen, 8/19/11)

SSC Example Risk Assessment

The CIR Science and Support Committee (SSC) provided an "example of a product specific risk assessment" for the use of Acrylates/C10-30 Alkyl Acrylates Crosspolymer polymerized in benzene in a leave-on product. The example was calculated assuming the use of a body lotion containing 0.4% Acrylates/C10-30 Alkyl Acrylates Crosspolymer containing 0.41% residual benzene. The latter (0.41% benzene) represents the highest benzene concentration in 40 batches of Acrylates/C10-30 Alkyl Acrylates Crosspolymer polymerized in benzene, as reported by a supplier.

These and the other assumptions used to calculate SSC's example exposure assessment are listed below.

- 50th percentile product use = 7.63 g body lotion used/use day
- 95th percentile product use = 16.83 g body lotion used/use day
- 0.4% Acrylates/C10-30 Alkyl Acrylates Crosspolymer in body lotion
- 0.41% benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer
- 10% benzene absorbed through the skin

Using these values, the SSC calculated the following exposure estimates:

- 50^{th} percentile = 12.5 µg/day
- 95^{th} percentile = 27.6 µg/day

They compared these values to a drinking water exposure range (2 to 20 µg/day) that corresponds to the range of drinking water concentrations (1 to 10 µg/liter) that the US EPA suggests represents a 10^{-6} lifetime cancer risk (1 to 10 µg/liter x 2 liters/day = 2 to 20 µg/day). Thus, the 95^{th} percentile exposure estimate calculated by the SSC exceeds the EPA drinking water range by about 38% (27.6 µg/day / 20 µg/day x 100 = 138%). The SSC then assumed that 10% of the benzene in the Acrylates/C10-30 Alkyl Acrylates Crosspolymer would evaporate during the manufacturing of the body lotion. If so, the SSC estimate would exceed the EPA's drinking water range by 24% (27.6 µg/day x 90% / 20 µg/day x 100 = 124%).

Risk Estimates Based on the SSC Assumptions

The EPA Integrated Risk Information System (IRIS) presents the oral slope factor for benzene as a range, based on the assumption that 100% benzene is absorbed after oral exposure. Specifically, the slope factor ranges from 1.5×10^{-5} to 5.5×10^{-5} $[\mu g/kg/day]^{-1}$. The EPA drinking water concentration range (1 to 10 µg/liter) representing a 10^{-6} lifetime cancer risk was calculated from the slope factor range, and rounding down the lowest concentration of the range to 1 µg/liter and rounding up the highest concentration to 10 µg/liter.

General Equation:

Cancer Risk Estimate [unitless] = [%] benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer x [%] Acrylates/C10-30 Alkyl Acrylates Crosspolymer in body lotion x [g/day] body lotion x [%] benzene absorbed percutaneously x $[kg]^{-1}$ body weight x 10^{6} [µg/g] conversion factor x slope factor $[\mu g/kg/day]^{-1}$

Upper Bound Risk Estimates for 95^{th} Percentile Exposure

Using the EPA highest cancer slope factor in the range (5.5×10^{-5} $[\mu g/kg/day]^{-1}$) in accordance with the EPA risk assessment guidelines yields an upper bound lifetime cancer risk estimate of 2.2×10^{-5}, assuming 95^{th} percentile product use and 70 kg body weight:

- 0.41 % x 0.4 % x 16.83 g/day x 10% x 1/70 $[kg]^{-1}$ x 10^{6} µg/g x 5.5 x 10^{-5} $[µg/kg/day]^{-1}$ = 2.17 x 10^{-5}

This estimate (2.2 x 10^{-5}) is 22 times higher than the upper bound risk estimate considered to be *de minimis* (10^{-6}).

Assuming that 10% of the benzene evaporates during the product manufacturing process reduces the upper bound estimate to 2 x 10^{-5} (2.17 x 10^{-5} x 90% = 1.95 x 10^{-5}), which is still about 20 times higher than 10^{-6}.

The benzene concentration used may be as high as 0.5% in Acrylates/C10-30 Alkyl Acrylates Crosspolymer, rather than 0.41%. Assuming 0.5% benzene increases the risk estimates by 22% (0.5/0.41 x 100 = 121.95%). Thus, the upper bound risk estimate associated with the 95th percentile exposure is 2.7 x 10^{-5} (2.17 x 10^{-5} x 122% = 2.65 x 10^{-5}) without evaporation during manufacturing, and 2.4 x 10^{-5} with 10% evaporation during the manufacturing process (2.17 x 10^{-5} x 122% x 90% = 2.38 x 10^{-5}). These values are 24 to 27 times higher than 10^{-6}.

Using the lowest EPA cancer slope factor in the range (1.5 x 10^{-5} $[µg/kg/day]^{-1}$) yields upper bound lifetime cancer risk estimates of 5.9 x 10^{-6} and 7.2 x 10^{-6} for 0.41% and 0.5% benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer, respectively:

- 0.41 % x 0.4% x 16.83 g/day x 10% x 1/70 $[kg]^{-1}$ x 10^{6} µg/g x 1.5 x 10^{-5} $[µg/kg/day]^{-1}$ = 5.91 x 10^{-6}
- 0.5 % x 0.4% x 16.83 g/day x 10% x 1/70 $[kg]^{-1}$ x 10^{6} µg/g x 1.5 x 10^{-5} $[µg/kg/day]^{-1}$ = 7.21 x 10^{-6}

Assuming that 10% of the benzene evaporates during the product manufacturing process reduces the upper bound estimate to 5.3 x 10^{-6} (5.91 x 10^{-6} x 90% = 5.32 x 10^{-6}) for 0.41% benzene and 6.5 x 10^{-6} (7.21 x 10^{-6} x 90% = 6.49 x 10^{-6}) for 0.5% benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer, as supplied. These values are 5 to 7 times higher than 10^{-6}.

Upper Bound Risk Estimates for 50th Percentile Exposure:

Risk assessments often include calculating risk estimates for 50th percentile exposures for comparison with 95th percentile exposures. Using US EPA's highest cancer slope factor in the range (5.5 x 10^{-5} $[µg/kg/day]^{-1}$):

- 0.41 % x 0.4 % x 7.63 g/day x 10% x 1/70 $[kg]^{-1}$ x 10^{6} µg/g x 5.5 x 10^{-5} $[µg/kg/day]^{-1}$ = 9.83 x 10^{-6}

This estimate is about 10 times higher than the upper bound risk estimate considered to be *de minimis* (10^{-6}).

Assuming that 10% of the benzene evaporates during the product manufacturing process reduces the upper bound estimate to 8.8 x 10^{-6} (9.83 x 10^{-6} x 90% = 8.85 x 10^{-5}), which is about 9 times higher than 10^{-6}.

Assuming 0.5% benzene increases the risk estimates by 22%. Thus, the upper bound risk estimate associated with 50th percentile exposure is 1.2 x 10^{-5} (9.83 x 10^{-6} x 122% = 1.2 x 10^{-5}) without evaporation during manufacturing, and 1.1 x 10^{-5} with 10% evaporation during the manufacturing process (9.83 x 10^{-6} x 122% x 90% = 1.08 x 10^{-5}). These values are 11 to 12 times higher than 10^{-6}.

Using US EPA's lowest cancer slope factor in the range (1.5 x 10^{-5} $[µg/kg/day]^{-1}$) yields an upper bound lifetime cancer risk estimates of 2.7 x 10^{-6} and 3.3 x 10^{-6} for 0.41% and 0.5% benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer, respectively:

- 0.41 % x 0.4% x 7.63 g/day x 10% x 1/70 $[kg]^{-1}$ x 10^{6} µg/g x 1.5 x 10^{-5} $[µg/kg/day]^{-1}$ = 2.68 x 10^{-6}
- 0.5 % x 0.4% x 7.63 g/day x 10% x 1/70 $[kg]^{-1}$ x 10^{6} µg/g x 1.5 x 10^{-5} $[µg/kg/day]^{-1}$ = 3.27 x 10^{-6}

Assuming that 10% of the benzene evaporates during the product manufacturing process reduces the upper bound estimate to 2.4 x 10^{-6} (2.68 x 10^{-6} x 90% = 2.41 x 10^{-6}) for 0.41% benzene and 2.9 x 10^{-6} (3.27 x 10^{-6} x 90% = 2.94 x

10^{-6}) for 0.5% benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer, as supplied. These values are about 3 times higher than 10^{-6}.

Evaporation of Benzene During the Manufacturing Process

Using the highest EPA cancer slope factor in their range (5.5×10^{-5} [µg/kg/day] $^{-1}$), assuming 0.41% benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer, 95th percentile product use, and 10% percutaneous absorption, about 95% evaporation during the manufacturing process would yield a cancer risk estimate of 10^{-6}:

- 0.41 % x 0.4 % x 16.83 g/day x 10% x 1/70 [kg]$^{-1}$ x 10^{6} µg/g x 5.5×10^{-5} [µg/kg/day]$^{-1}$ x 5% = 1.08×10^{-6}

Using the highest EPA cancer slope factor and assuming 50th percentile product use and 10% percutaneous absorption, about 89% evaporation during the manufacturing process would yield a cancer risk estimate of 10^{-6}:

- 0.41 % x 0.4 % x 7.63 g/day x 10% x 1/70 [kg]$^{-1}$ x 10^{6} µg/g x 5.5×10^{-5} [µg/kg/day]$^{-1}$ x 11% = 1.08×10^{-6}

Using the lowest EPA cancer slope factor in their range (1.5×10^{-5} [µg/kg/day] $^{-1}$), assuming 0.41% benzene in Acrylates/C10-30 Alkyl Acrylates Crosspolymer, 95th percentile product use, and 10% percutaneous absorption, about 83% evaporation during the manufacturing process would yield a cancer risk estimate of 10^{-6}:

- 0.41 % x 0.4 % x 16.83 g/day x 10% x 1/70 [kg]$^{-1}$ x 10^{6} µg/g x 1.5×10^{-5} [µg/kg/day]$^{-1}$ x 17% = 1.01×10^{-6}

Using the lowest EPA slope factor in their range, assuming 10% percutaneous absorption and 50th percentile product use, about 63% evaporation during the manufacturing process would yield a cancer risk estimate of 10^{-6}:

- 0.41 % x 0.4 % x 7.63 g/day x 10% x 1/70 [kg]$^{-1}$ x 10^{6} µg/g x 1.5×10^{-5} [µg/kg/day]$^{-1}$ x 37% = 9.9×10^{-7}

Using the highest EPA cancer slope factor and assuming 1% percutaneous absorption and 95th percentile product use, about 50% evaporation during the manufacturing process would yield a cancer risk estimate of 10^{-6}:

- 0.41 % x 0.4 % x 16.83 g/day x 1% x 1/70 [kg]$^{-1}$ x 10^{6} µg/g x 5.5×10^{-5} [µg/kg/day]$^{-1}$ x 50% = 1.08×10^{-6}

DEA

Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Monice M. Fiume *MMF*
Senior Scientific Analyst/Writer

Date: Setpember 16, 2011

Subject: Wave 2 memo - Diethanolamine

DEA can be present as an impurity in DEA condensates. Updated concentration of use data were received that gives the amount of DEA present based on the DEA specifications for DEA condensates and the concentration of use of those condensates in cosmetic formulations.

The concentrations of DEA present in leave-on and rinse-off formulations are reported as 0.13 and 0.64%, respectively.

These data are included with this Wave 2 submission.

1101 17th St., NW, Suite 412 Washington, DC 20036-4702
Phone 202.331.0651 FAX 202.331.0088 http://www.cir-safety.org

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 13, 2011

SUBJECT: Updated Concentration of Use Information by FDA Product Category: Diethanolamine and Diethanolamine from the use of DEA Condensates

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Concentration of Use by FDA Product Category
Diethanolamine and Diethanolamine from use of DEA Condensates

Product Category	DEA Concentration of Use	Calculated DEA Concentration from use of DEA Condensates*
Baby shampoo		0.2%
Bath oils, tablets and salts		0.01%
Shampoos (noncoloring)	0.03-0.3%	0.3-0.64%
Tonics, dressings and other hair grooming aids	0.008%	
Other hair preparations (noncoloring)		0.03%
Bath soaps and detergents	0.009%	0.1-0.5%[1]
Shaving cream (aerosol, brushless and lather)	0.06%	0.11%
Other shaving preparation		0.11%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)		0.1-0.13%
Face and neck creams, lotions and powders		0.05%
Body and hand creams lotions and powders		0.04%
Moisturizing creams, lotions and powders	0.06%	

*DEA concentrations in products calculated based on the DEA specification for the DEA condensate added to the product and the amount of DEA condensate added to the product.
[1]0.5% DEA from a DEA condensate in a liquid hand soap

Updated September 13, 2011: Table updated from the Ethanolamine table (MEA, DEA, TEA) last updated November 10, 2011.

Formaldehyde

Cosmetic Ingredient Review
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CIR

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Director, CIR
Date: September 16, 2011
Subject: Wave 2: Information re formaldehyde/methylene glycol.

We have received a letter from David Steinberg addressing the use of formaldehyde/methylene glycol that describes testing of nail hardeners and reporting on current use concentrations. A redacted version of the test findings is also provided He also comments on the possible involvement of formaldehyde in the cases that Dr. Belsito mentioned at the June meeting.

Government actions taken since June also are provided:

1. FDA's warning letter to Brazilian Blowout
2. OSHA action to cite Florida manufacturers and distributors of hair smoothing products
3. New York State's letter to FDA, citing CIR's findings, and asking FDA to prohibit formaldehyde in hair smoothing products that are heated.

What we have not received as of this date is anything from the Professional Keratin Smoothing Council.

1101 17th St., NW, Suite 412 Washington, DC 20036-4702
Phone 202.331.0651 FAX 202.331.0088 http://www.cir-safety.org

Steinberg & Associates, Inc.
16 Mershon Lane, Plainsboro, NJ 08536
Ph. (609) 799-1575 Fax (609) 799-5271
Email: Davidpreserve@comcast.net

September 5, 2011

Alan Andersen, PhD Director
Cosmetic Ingredient Review
1101 17th St. N. W. Suite 412
Washington D. C. 20036-4702

Dear Dr. Andersen:

I have been requested by the Nail Manufacturers Council (NMC) to assist it in responding to the CIR on the following matters. These comments supplement the filing by the NMC dated May 11, 2011. At the recent CIR meeting and through its Draft report, the Panel requested additional data on methylene glycol use in nail hardeners. Formaldehyde, as noted in the report, is an anhydrous gas that is not used and has never been used, as an ingredient in nail hardeners or any known cosmetics.

Responses to CIR Informational Requests

There were two specific areas in which the Panel requested additional information.

1. Two clinical patients using the same brand of nail hardener, Quimica Allemana, imported from Colombia, experienced eyelid dermatitis which, if related to the use of a nail hardener, would more likely result from rubbing the eyelid before the nail coating on the nail plate was completely dry, rather than from vapors. NMC obtained samples of this from Amazon and had them analyzed (at an outside lab-report and explanation attached) in comparison to a commercial US manufactured product. As the Quimica Allemana line was unknown to the NMC, a search was first conducted on its website to find out where it could be purchased. While we presume that the product purchased from Amazon and tested for NMC was genuine and produced by Quimica Allemana, it should also be noted that its website warns "**Beware of the fake product** Counterfeiters do not stop doing identical imitations of our product."

   The NMC is ill-equipped to state what caused the reaction in these two patients, information on which is limited and was brought forward just before the last CIR Expert Panel meetings. However, the scientists working with the NMC are confident in stating what was likely not the cause i.e. vapors from nail hardeners.

Are there skin allergies to formalin caused other than by occlusive entrapment of formalin against the skin? Probably not! These scientists working with NMC also find themselves at a great disadvantage dealing with two, excuse the expression, anecdotal last minute cases, in the face of years of there being no reported incidents of such reactions from consumers using products of the NMC members.

The Quimica Allemana label indicated these ingredients: Tosylamide/Formaldehyde Resin, Formaldehyde, Camphor, Nitrocellulose, Castor Oil, N-Butyl Alcohol, MEK, Ethyl Acetate, Butyl Acetate, Amyl Acetate. This is clearly mis-labeled, as the product is intended to be a free flowing liquid and the ingredients could, therefore, not possibly be in descending order of predominance as is required in the US (and Colombia!) for this to be the case.

The comments presented at the meeting and the draft report indicated both "patients tested negative to 1% formaldehyde." In reviewing the ingredients, Castor oil is present. I have had issues with dermatitis caused by castor oil in the past, usually lipsticks. In testing, the culprit was usually propyl gallate which is added as an anti-oxidant to the castor and doesn't show up on ingredient listings. The last time this was raised with me was by a dermatologist who, having a patient with this problem, spoke to me in private at the Hershey Conference. She confirmed later to me that her patient was sensitive to propyl gallate and that the lipstick did indeed contain this from the castor oil. When the patient switched lipsticks, the problem disappeared.

It does not make sense to question the safety of methylene glycol in Nail Hardeners based on two cases raised at the last minute at the meeting, when historically there have been no issues. The use of methylene glycol is being questioned when there is evidence that it likely did not cause the reaction.

2. The second concern was for a better understanding of concentrations of methylene glycol used in current nail hardeners. A survey was undertaken of these marketers in the US: OPI, CND, Orly, Nail Tek, Jessica Cosmetics, American International, Nailtiques, Sally Hansen, Essie and one foreign company who sells here, namely Mavala (from Switzerland). Some brands did not use any methylene glycol. Those that did, used less than 2% (amount of 37% "formalin" added). We also confirmed with the suppliers to the industry that levels of "formalin" used were less than 2%, e.g., 5% methylene glycol times 37% equals 1.85%.

<u>Comments</u>

It is my opinion, and also that of other scientists, that the nomenclature must be changed to reflect the true chemistry. Just because the terms formaldehyde and methylene glycol are used interchangeably doesn't make the practice accurate or

proper. On behalf of the Nail Manufacturers Council, I submitted the INCI name *methylene glycol* for addition to the INCI Dictionary in 2007 and the name was issued in 2008.

I invite the CIR to write to PCPC requesting that the monograph on Formaldehyde be removed from the INCI Dictionary. Formaldehyde is not a cosmetic ingredient. Further, under the Methylene glycol monograph the alternative name should be *formalin*. The NMC has not pushed for the switch to the correct nomenclature until all of the issues are resolved, but would appreciate your support in doing so now. Being correct scientifically should not be seen as a way to deceive the public. Truth in advertising and labeling demands accurate chemical terminology.

Also, the comment that formaldehyde (gas) is dissolved in water is not correct. Formaldehyde reacts with water to form methylene glycol. For clarity, this is not the same as sugar being dissolved in water, leaving you with sugar in water. Formaldehyde gas reacts with water to produce methylene glycol. A chemical reaction should not be confused with mere dissolution.

Significantly, the "equilibrium" reaction strongly favors methylene glycol, with only traces of formaldehyde present in a very low PPM range (See NMC May 11, 2011 Comments filed with CIR). The equilibrium reaction results in more than 99.92% MG and less than 0.08% HCHO being present at 25 C. Significantly, unlike hair smoothing products, no heat is applied in the application of nail hardeners as they are flammable. Heat, of course, drives the equilibrium reaction to the left, towards HCHO. Without the addition of heat, extremely minimal HCHO (gas), if any, is released.

Therefore, nail hardening products should be labeled with the correct INCI designation (methylene glycol). Moreover, to make certain there is no misunderstanding among users, a cautionary statement could be required of manufacturers by the CIR that states "if you are sensitive to formaldehyde, you may be sensitive to this product."

Because the terms formaldehyde and formalin were, and are, used interchangeably, safety reports on "formaldehyde" are, therefore, not clearly defined as to what actually was tested, namely the anhydrous gas (truly formaldehyde) or formalin (the "commercial" name for methylene glycol solution). Methods to analyze for "formaldehyde" are typically run in water and, therefore, are clearly measuring methylene glycol, but reporting it as "formaldehyde".

Commonly used tests are not specific for methylene glycol or formaldehyde. Only C-13 NMR is specific for methylene glycol. Most common tests (the acetyl acetone method, which is the method used in cosmetics, or the 2,4-Dinitrophenylhydrazine used industrially) can be reactions of any aldehyde or any

ketone, not just “formaldehyde.” Frequently the levels of “formaldehyde” reported in such tests are incorrect because of these non-specific reactions. For example, propylene glycol will react with the Nash reagent and, therefore, test positive for “formaldehyde” when none really exists. Using the proposed term “formaldehyde equivalents” as the CIR has proposed merely muddies the water further. **It is far better to report the amount calculated as anhydrous formaldehyde.**

Regarding the “formaldehyde” levels in hardeners, the amount of formalin used ranges from 2% to 5%. Formalin contains 37% formaldehyde, so the actual levels of “formaldehyde” range between 0.7% and 1.85%. Again, because of the equilibrium reaction, the actual “formaldehyde” number is much lower, in fact, in the low PPM range. (See NMC May 11, 2011 Comments Filed with the CIR)

Additional Comments

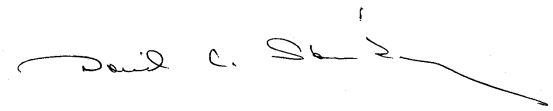
The significant decrease in reported uses of Formaldehyde in VCRP is the result of a switch in the early eighties, from its use as a preservative, to the mixture of Methylchloroisothiazolinone and Methylisothiazolinone. This occurred especially in rinse off hair care products.

Nail shields are not supplied with nail hardeners as both consumer and professional users do not use them. Applying the nail hardener is just like applying nail polish so the person applying the product only puts it on the nail and, as this is commonly done, it is very easy to avoid skin contact.

Comments about adverse reactions obtained from the internet and personal blogs should be deleted. They are of unknown source and honesty and should not be part of a scientific study.

Thank you for the opportunity to supplement the record and comment on your draft report. I look forward to seeing again in September at the next meeting.

Regards,



David C. Steinberg

cc: Personal Care Products Council

Micro Quality Labs, Inc.

Specializing in Pharmaceutical and Cosmetic Testing
3200 N. San Fernando, Burbank, CA 91504
(818) 845-0070 • Fax: (818) 845-0030
E-Mail: Karine@MicroQualityLabs.com

OPI Product Inc.
Attention: Rohani Efendi
13056 Saticoy St.
N. Hollywood, CA 91605

PO# 11374

CERTIFICATE OF ANALYSIS

Sample Name: [redacted] A
Code: [redacted]
Batch: [redacted]
Sample Description: Finished Product
MQL accession# 110707-0002R
Sample Date: 07/06/11
Test Method: MQLTM-0078
Revision Date: N/A

Formaldehyde by HPLC – Visible Absorption

An initial dilution of 1:11 (1g. sample + 9mL water + 1mL acetonitrile) was mixed for 20 minutes on a mechanical shaker. A 0.4mL aliquot of the initial dilution was diluted further and derivatized with 2,4-dinitrophenylhydrazine (DNPH). The resulting test solution were filtered through a 0.45 micron PTFE filter and analyzed by HPLC with UV detection at 354nm. The detection limits were adjusted for the final dilution.

ANALYSIS:	RESULTS:	DETECTION LIMIT:
Formaldehyde:	1.9%	<0.05ppm

Date Derivatized: 08/03/11
Date Analyzed: 08/03/11

Quality Control Summary

Sample ID: [redacted] A

Analyte:	Sample Result:
Formaldehyde	1.9%

Approved By:
Danielle Bartoli
Document Control 08/05/11

A.P
Senior Chemist 08/05/11

Comment: Retest

Micro Quality Labs, Inc.

Specializing in Pharmaceutical and Cosmetic Testing
3200 N. San Fernando, Burbank, CA 91504
(818) 845-0070 • Fax: (818) 845-0030
E-Mail: Karine@MicroQualityLabs.com

OPI Product Inc.
Attention: Rohani Efendi
13056 Saticoy St.
N. Hollywood, CA 91605

PO# 11374

CERTIFICATE OF ANALYSIS

Sample Name: [redacted] B
Code: [redacted]
Sample Description: Finished Product
MQL accession# 110707-0001R
Sample Date: 07/06/11
Test Method: MQLTM-0078
Revision Date: N/A

Formaldehyde by HPLC – Visible Absorption

An initial dilution of 1:11 (1g. sample + 9mL water + 1mL acetonitrile) was mixed for 20 minutes on a mechanical shaker. A 0.4mL aliquot of the initial dilution was diluted further and derivatized with 2,4-dinitrophenylhydrazine (DNPH). The resulting test solution were filtered through a 0.45 micron PTFE filter and analyzed by HPLC with UV detection at 354nm. The detection limits were adjusted for the final dilution.

ANALYSIS:	RESULTS:	DETECTION LIMIT:
Formaldehyde:	2.0%	<0.05ppm

Date Derivatized: 08/03/11
Date Analyzed: 08/03/11

Quality Control Summary

Sample ID: [redacted] B

Analyte:	**Sample Result:**
Formaldehyde	2.0%

Approved By:
Danielle Bartoli
Document Control 08/05/11

A.P
Senior Chemist 08/05/11
Sm for A.P.

Comment: Retest

Department of Health and Human Services

Public Health Service
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

WARNING LETTER

AUG 22 2011

VIA OVERNIGHT-DELIVERY
RETURN RECEIPT REQUESTED

Mr. Mike Brady, CEO
GIB, LLC dba Brazilian Blowout
6855 Tujunga Avenue
North Hollywood, CA 91605-6312

Re: 207094

Dear Mr. Brady:

The U.S. Food and Drug Administration (FDA) has reviewed the regulatory status of your product, Brazilian Blowout Acai Professional Smoothing Solution (Brazilian Blowout). As Brazilian Blowout is intended to be applied to the human body for cleansing, beautifying,promoting attractiveness, or altering the appearance, it is a cosmetic within the meaning of Section 201(i) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(i)]. As described below, Brazilian Blowout is adulterated within the meaning of Section 601 (a) of the Act [21 U.S.C. § 361 (a)] and is misbranded within the meaning of Section 602(a) of the Act [21 U.S.C. § 362(a)]. It is a violation of Section 301(a) of the Act [21 U.S.C. § 331(a)] to introduce or deliver for introduction into interstate commerce any cosmetic that is adulterated or misbranded. You can find copies of the Act and its implementing regulations through links on FDA's home page at http://www.fda.gov[1].

Adulterated Cosmetic

Under Section 601(a) of the Act [21 U.S.C. § 361(a)], a cosmetic is adulterated if it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or, under such conditions of use as are customary or usual. Brazilian Blowout is an adulterated cosmetic because it bears or contains a deleterious substance that may render it injurious to users under the conditions of use prescribed in your labeling. Specifically, based on FDA sample analysis, Brazilian Blowout contains methylene glycol, the liquid form of formaldehyde, which, under the conditions of use prescribed in the labeling, releases formaldehyde when hair treated with the product is heated with a blow dryer and then with a hot flat iron. Methylene glycol is a deleterious substance, which at the levels present in this product, may harm users under the conditions of use prescribed in the labeling thereof. FDA analysis of approximately 50 mg samples of Brazilian Blowout confirmed the presence of methylene glycol, the liquid form of formaldehyde, at levels ranging from 8.7 to 10.4%.

The primary route of exposure to formaldehyde, when using Brazilian Blowout under the conditions of use prescribed in the labeling, is through inhalation. Formaldehyde is a highly reactive chemical that readily reacts with biological tissues, particularly the mucous tissues lining the respiratory tract and the eyes. Adverse events have reported the following injuries associated with Brazilian Blowout: eye disorders (irritation, increased lacrimation, blurred vision, hyperaemia); nervous system disorders (headache, burning sensation, dizziness, syncope), and respiratory tract (dyspnea, cough, nasal discomfort, epistaxis, wheezing, rhinorrhea, throat irritation, nasopharyngitis). Other reported symptoms included nausea hypotrichosis, chest pain, chest discomfort, vomiting, and rash.

Brazilian Blowout is targeted primarily for use by salon professionals in a salon setting. The product may also be used in home salon settings as Brazilian Blowout is also available for purchase in beauty retail stores and via the internet by the general public.

Misbranded Cosmetic

In addition, under Section 602(a) of the Act [21 U.S.C. § 362(a)], a cosmetic is misbranded if its labeling is false or misleading in any particular. Section 201(n) of the Act [21 U.S.C. § 321(n)] provides that, in determining whether a product's labeling or advertising is misleading "there shall be taken into account (among other things) the extent to which the labeling or advertising fails to reveal facts material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."

Brazilian Blowout is misbranded because its label and labeling (including instructions for use) makes misleading statements regarding the product's ingredients and fails to reveal material facts with respect to consequences that may result from the use of the product. Specifically, Brazilian Blowout contains the liquid form of formaldehyde, methylene glycol; however, the product label declares that the product contains "No Formaldehyde" or is "Formaldehyde Free." This declaration renders your product misbranded because it is a false and misleading statement. In addition, the failure to include information about the release of formaldehyde into the air during the heating process on the product's label or labeling makes your product misbranded because you fail to reveal material facts with respect to consequences that may result from the use of your product under the conditions of use prescribed in the labels or labeling.

The violations cited in this letter are not intended to be an all-inclusive list of the violations that exist in connection with your product. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility as a manufacturer to ensure that the products your firm markets are safe and otherwise in compliance with all applicable legal and regulatory requirements.

You should take prompt action to correct the violations cited in this letter. Failure to do so may result in enforcement action without further notice, including, but not limited to, seizure and/or injunction.

Please advise this office in writing within fifteen (15) working days from your receipt of this letter as to the specific steps you have taken to correct the violations noted above and to assure that similar violations do not occur in the future. Your response should include any documentation necessary to show that correction has been achieved. If you cannot complete all corrections before you respond, please explain the reason for your delay and the date by which each item will be corrected and documented.

Please direct your written reply to Rob Genzel Jr., Food and Drug Administration, Center for Food Safety and Applied Nutrition, 5100 Paint Branch Parkway, Office of Compliance (HFS-608), Division of Enforcement, College Park, Maryland 20740-3835.

Sincerely,

/S/
Michael W. Roosevelt
Acting Director
Office of Compliance
Center for Food Safety
and Applied Nutrition

OSHA Regional News Release

U.S. Department of Labor
Office of Public Affairs **Region 4**

Region 4 News Release: 11-1314-ATL (431)
Sept. 8, 2011
Contact: Michael D'Aquino Michael Wald
Phone: 404-562-2076 404-562-2078
Email: d'aquino.michael@dol.gov wald.michael@dol.gov

US Department of Labor's OSHA cites Florida manufacturers and distributors of hair products containing formaldehyde for health violations

Companies failed to protect workers, warn product users of hazards

ATLANTA – The U.S. Department of Labor's Occupational Safety and Health Administration has cited two Florida manufacturers and two Florida-based distributors of hair products containing formaldehyde for 16 health violations involving alleged failures to protect their employees from possible formaldehyde exposure and to communicate with the products' users, such as salons and stylists, about the hazards of formaldehyde exposure. Proposed penalties for the companies total $49,200.

"Employers are responsible for identifying the risks associated with producing and using these hair products, as well as for taking appropriate measures to ensure that they protect their own employees and other workers who may be using their products, such as stylists, from any potential hazards," said Cindy Coe, OSHA's regional administrator in Atlanta.

OSHA's inspections were initiated based on a referral by Oregon's Occupational Safety and Health Division, which tested more than 100 product samples at 50 salons using hair smoothing or straightening products. Some products causing formaldehyde exposure were traced back to the Florida manufacturers and distributors. Formaldehyde can irritate the eyes and nose, and cause coughing and wheezing. It is a sensitizer, which means that it can cause allergic reactions of the lungs, skin and eyes, such as asthma, rashes and itching. It also has been linked to cancer.

Both M&M International Inc. in Delray Beach, a distributor of the straightening hair product "Marcia Teixeira," and Copomon Enterprises in Boca Raton, a distributor of the keratin-based hair product "Keratin Complex Smoothing Therapy," have been cited for three serious violations and fined $12,600 each for failing to ensure that material safety data sheets reflected the content of formaldehyde in the products or the hazards associated with formaldehyde exposure, as well as for failing to develop a written hazard communication program for their own employees. A serious violation occurs when there is substantial probability that death or serious physical harm could result from a hazard about which the employer knew or should have known.

Pro Skin Solutions Inc. in Orlando, a manufacturer of keratin-based products used for hair straightening, has been cited for five serious violations with penalties of $15,000. Violations include failing to establish a written respiratory protection plan, provide an emergency eyewash station, develop appropriate procedures to protect employees in the event of an emergency and develop or implement a written hazard communication program. The company also failed to address formaldehyde exposure and inhalation hazards, including possible cancer-causing effects, on material safety data sheets for the formaldehyde-containing products.

Additionally, Pro Skin Solutions has been cited for two other-than-serious violations with no monetary penalties for failing to maintain air sampling records and provide written procedures for evaluating chemical hazards. An other-than-serious violation is one that has a direct relationship to job safety and health, but probably would not cause death or serious physical harm.

Keratronics Inc. in Coral Springs, a manufacturer of keratin-based products used for hair straightening, has been cited for three serious violations with penalties of $9,000 for failing to provide an eyewash station for employees using corrosive products, evaluate the hazards of keratin-based products for development of the material safety data sheets, and develop or maintain a written hazard communication program on handling chemicals such as timonacic acid, formalin, acetic acid and hydrolyzed keratin.

All manufacturers, importers and distributers are required by OSHA standards to identify formaldehyde on any product that contains more than 0.1 percent formaldehyde, either as a gas or in a solution that can release formaldehyde at concentrations greater than 0.1 part per million. The material safety data sheet that comes with the product also must include this information, as well as explain why the chemical is hazardous, what harm it can cause, what protective measures should be taken and what to do in an emergency. The sheets are used by employers to determine products' potential health hazards and methods to prevent worker exposure.

Federal OSHA issued a hazard alert earlier this year to hair salon owners and employees about potential formaldehyde exposure resulting from working with some hair smoothing and straightening products. It can be viewed at http://www.osha.gov/SLTC/formaldehyde/hazard_alert.html.

In addition, the U.S. Food and Drug Administration recently issued a warning letter to GIB LLC in North Hollywood, Calif., doing business as Brazilian Blowout, concerning misbranding relating to formaldehyde. That letter is available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm270809.htm.

Keratronics, M&M International and Copomon Enterprises were inspected by OSHA's Fort Lauderdale Area Office, 1000 S. Pine Island Road, Suite 100, Fort Lauderdale, Fla. 33324; telephone 954-424-0242. Pro Skin Solutions was inspected by OSHA's Tampa Area Office, located at 5807 Breckenridge Parkway, Suite A, Tampa, Fla. 33610; telephone 813-626-1177. To report workplace incidents, fatalities or situations posing imminent danger to workers, call the agency's toll-free hotline at 800-321-OSHA (6742).

The companies have 15 business days from receipt of the citations and proposed penalties to comply, request a conference with OSHA's area director or contest the findings before the independent Occupational Safety and Health Review Commission.

Under the Occupational Safety and Health Act of 1970, employers are responsible for providing safe and healthful workplaces for their employees. OSHA's role is to ensure these conditions for America's working men and women by setting and enforcing standards, and providing training, education and assistance. For more information, visit http://www.osha.gov.

###

OSHA News Release - Table of Contents

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U.S. Department of Labor | Occupational Safety & Health Administration | 200 Constitution Ave., NW, Washington, DC 20210
Telephone: 800-321-OSHA (6742) | TTY: 877-889-5627

www.OSHA.gov

NEW YORK
state department of
HEALTH

Nirav R. Shah, M.D., M.P.H.
Commissioner

Sue Kelly
Executive Deputy Commissioner

August 30, 2011

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Commissioner Hamburg:

I write to express my concern about the use of formaldehyde in some keratin-based hair smoothing products sold in New York State and elsewhere in the country. The continued availability of products containing high levels of formaldehyde poses a potentially significant health concern to both hair salon workers and consumers. New scientific information concerning the safety of formaldehyde in these products, including a report by the Cosmetic Ingredient Review (CIR) Expert Panel and the revised classification on the carcinogenicity of formaldehyde by the National Toxicology Program (NTP), highlight the serious public health risks associated with the use of these products. I respectfully request that the U.S. Food and Drug Administration (FDA) classify as "adulterated", all hair smoothing products that contain formaldehyde or formaldehyde equivalents. These adulterated products should be prohibited from interstate commerce in accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Hair smoothing products are readily available to the general public through hair salons and on the internet. The New York State Department of Health recently conducted an internet search and found more than 150 keratin-based professional use hair smoothing products for sale in the United States from 51 companies. This search also revealed the emergence of new keratin-based hair smoothing products that are being marketed for purchase and use by the general public for at-home treatments.

In response to health-complaints from workers and consumers, and emerging data on the presence of high levels of formaldehyde in some of these products, the FDA asked the CIR in 2010 to review the safety of formaldehyde in hair smoothing products. This review was supported by industry trade groups which provided technical comments on a draft document that the CIR released in March 2011. The CIR has reviewed and published safety assessments on formaldehyde in cosmetics since 1984.

On July 8, 2011 the CIR released the safety assessment entitled "Revised Tentative Amended Report: Formaldehyde and Methylene Glycol" (see: http://www.cir-safety.org/staff_files/Formal062011tr.pdf). The announcement on the CIR's website for this report summarizes the conclusions of the CIR's Expert Panel (see: http://www.cir-safety.org/staff_files/results.pdf). The conclusions include a determination that formaldehyde and formaldehyde equivalents "are safe for use in cosmetics applied to the skin when formulated for minimal effective concentration, but in no case should formaldehyde equivalents exceed

0.074%." However, the CIR's Expert Panel also determined that the use of formaldehyde as an ingredient in a product intended to be heated is uniquely different from its use in other cosmetics and that formaldehyde and formaldehyde equivalents "are unsafe for use in hair smoothing products, the use of which involves application of high temperatures."

The term "formaldehyde equivalents" refers to the different chemical forms of formaldehyde in water, such as methylene glycol, that are released as formaldehyde during use. The CIR's Expert Panel noted that "because the presence of methylene glycol ensures that formaldehyde will be present, such a product with a 'formaldehyde-free' label should be considered to be misbranded under the provisions of the FD&C Act."

People who are exposed to formaldehyde are at risk for a number of adverse short- and long-term health effects. The U.S. Department of Health and Human Services, Public Health Services, National Toxicology Program's 12th Report on Carcinogens now classifies formaldehyde as "known to be a human carcinogen." The report was released on June 10, 2011.

Product testing by the Oregon Department of Consumer and Business Services, Health Canada, and the European Directorate-General of Health and Consumer Affairs shows that some of these keratin-based hair smoothing products contain formaldehyde at levels as high as 11.8 percent. Some of the products that were found to contain formaldehyde were reportedly labeled as "formaldehyde-free." After the product is applied to the hair it must be heated with a blow dryer and then a 350 - 450 degree F flat iron. This heating process has been shown to generate high airborne concentrations of formaldehyde. During its investigation of these products, the US Occupational Safety and Health Administration (OSHA) tested air in hair salons for formaldehyde and found it to be present at levels greater than the OSHA acceptable limits. OSHA subsequently issued a Hazard Alert on this matter (see: http://www.osha.gov/SLTC/formaldehyde/hazard_alert.html).

The FD&C Act prohibits the interstate commerce of adulterated cosmetics [FD&C Act, sec. 301; 21 U.S.C. §331]. Keratin-based hair smoothing products that expose people to formaldehyde meet the FDA definition of an adulterated product in that they contain a substance that may cause harm during intended use. Exposures to formaldehyde could occur in the following circumstances:

- Salon workers, patrons and at-home users of these products are likely to inhale formaldehyde that is released to air when the products are applied and heated as directed by the manufacturer's label instructions.
- At-home users may apply and heat these products under conditions that could increase their exposure to airborne formaldehyde, such as within the confines of a small bathroom.
- Young children and infants may be exposed during at-home use.
- Formaldehyde can be absorbed through the skin. A typical application exposes the users' scalp to direct contact with formaldehyde in the product. Other unprotected skin areas of the user or salon worker may also be exposed.

The recent scientific information regarding the carcinogenicity of formaldehyde, the unprecedented concentration of formaldehyde in a cosmetic product, and the investigative data revealing the potential for formaldehyde exposure in excess of established safety limits clearly demonstrate the harmful nature of these hair smoothing products. In consideration of this information, I ask the FDA to prohibit the interstate commerce of all hair smoothing products that contain formaldehyde or formaldehyde equivalents.

Sincerely,

Nirav Shah

Nirav R. Shah, M.D., M.P.H.
Commissioner of Health

cc: Dr. Birkhead
Dr. Freed
Mr. Chinery
Ms. Franko

Silylates

Cosmetic Ingredient Review
Commitment . . . Credibility
Since 1976

C I R

September 16, 2011

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Wave 2 Data for the Draft Final Safety Assessment for Silylates

The Wave 2 packet for Silylates includes:

1) In response to a Panel concern, information on a product containing Trifluoropropyldimethyl/trimethylsiloxysilicate at 50% was provided by the Council. It contains a short overview of the manufacturing method and an analysis showing by gas chromatography that the end product does not contain any fluorine compounds or the initial materials.

2) Product information on a silica silylate product, including average particle size (5-15 μm). This is within what has been considered respirable. Is there a difference between liquid and dry (powder) cosmetic products when it comes to respiration?

3) Comment letter from the Synthetic Amorphous Silica and Silicate Industry (SASSI).

4) Comments on the Draft Final Safety Assessment by the Council and the Scientific Support Committee. Comments on the inhalation exposure studies in the Tentative Report and a re-survey of concentration of use.

5) A new Use Table has been developed with the new data from the Council.

6) The Council and SASSI pointed out a few inhalation studies that were in the ECETOC JACC, 2006 report on silica (CAS No. 7631-86-9) that do apply to surface-modified silylates. The sections of the ECETOC report that summarize these studies are provided and highlighted. [J-DCA TX104 refers to a silica silylate; Aerosil R974 refers to a silica dimethyl silylate.] These studies will be incorporated into the safety assessment.

   Because the Council and SASSI had comments on studies regarding the testing of quartz, the summaries of Reuzel et al. 1991 and Degussa 1987 are also highlighted. Since quartz is tested as a separate substance, and not incorporated into the silylate, the studies remain in the safety assessment.

7) Two studies showing the stability of trimethylsiloxysilicate in changing temperatures (-10ºC - 45ºC) and at high temperatures (45ºC). Trimethylsiloxysilicate was found to be thermally stable under these conditions.

NOTE: A re-examination of the source document of an acute inhalation study (Cabot Corporation, 2003) found that the particle size was 1.24 μm.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: August 19, 2011

SUBJECT: Product Information Trifluoropropyldimethyl/trimethylsiloxysilicate

Anonymous. 2011. Product information (Trifluoropropyldimethyl/trimethylsiloxysilicate 50% Cyclopentasiloxande solution).

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

August 19, 2011

Product Information

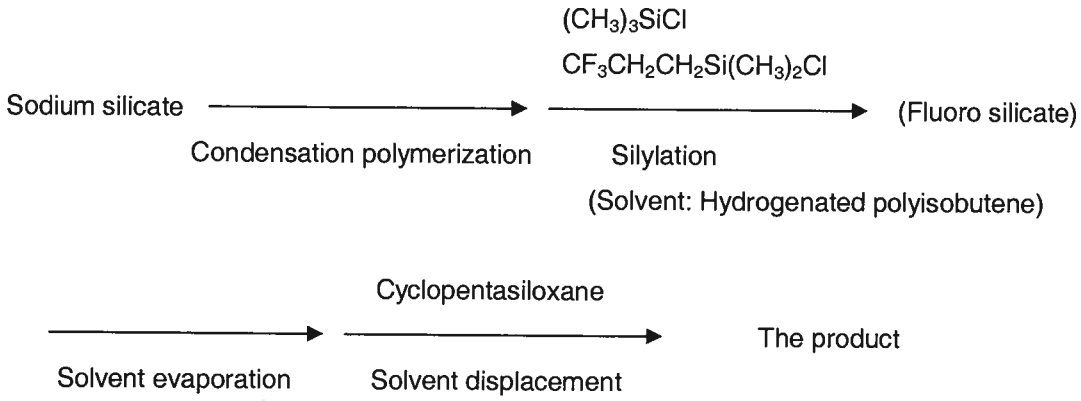
(Trifluoropropyldimethyl/trimethylsiloxysilicate 50% Cyclopentasiloxane solution)

1. Product Description

The product is a mixture of Fluoro-modified silicone MQ resin (Trifluoropropyldimethyl/trimethylsiloxysilicate) and Cyclopentasiloxane .

2. Manufacturing Process

The product is synthesized from sodium silicate, Trimethylchlorosilane ($(CH_3)_3SiCl$) and Trifluoropropyldimethylchlorosilane ($CF_3CH_2CH_2Si(CH_3)_2Cl$) as shown in the following flow.

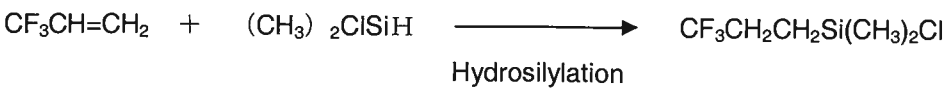


3. The possibility of containing fluorine compounds

Trifluoropropene ($CF_3CH=CH_2$) which is the initial material is possible to be contained in the product.

It is the fluorine compound which dose not chemically bonded to Si.

Trifluoropropyldimethylchlorosilicate is synthesized from Trifluoropropene by hydrosilylation shown below.



4. Gas chromatography

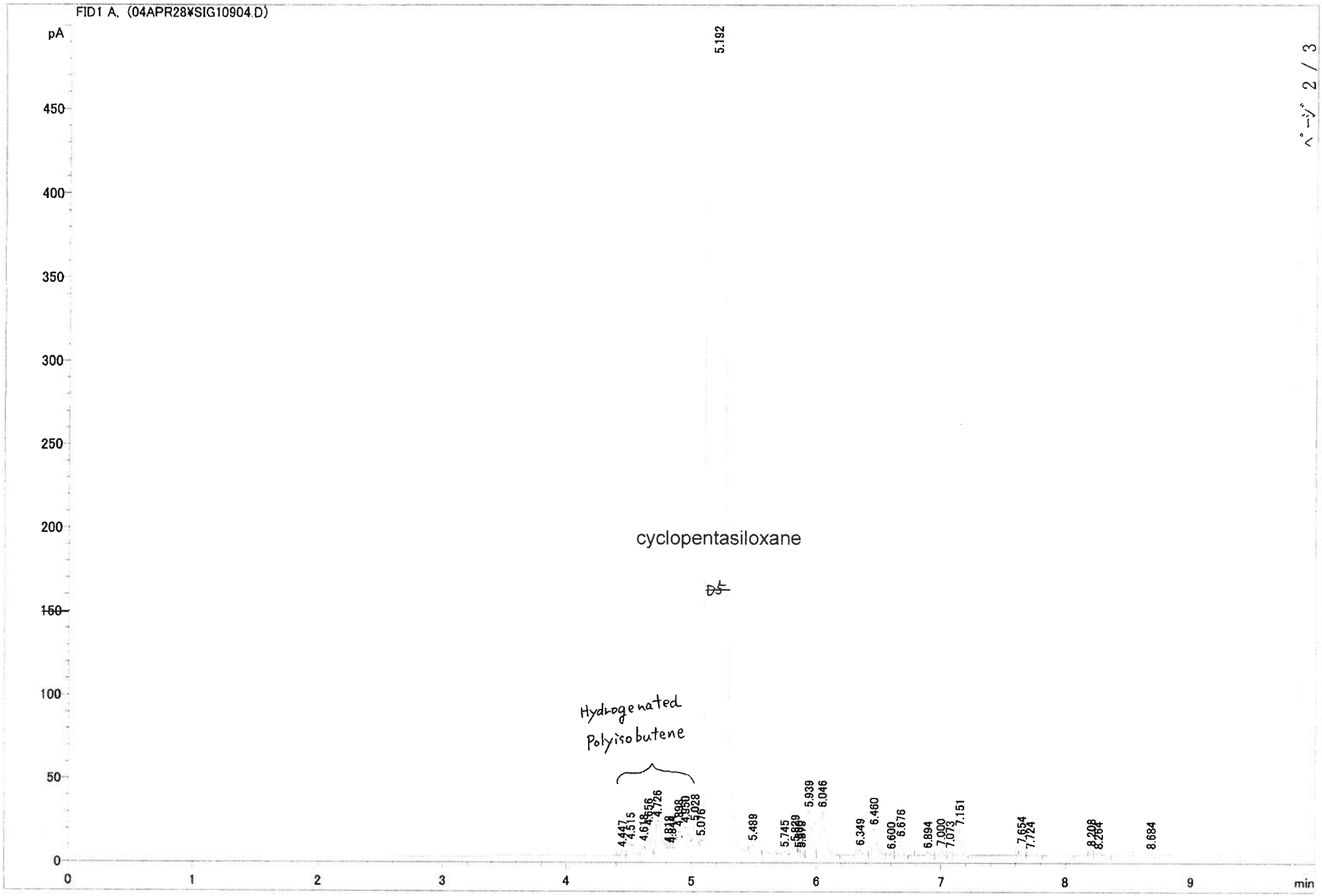
We analyzed the product to identify fluorine compounds and initial materials as referred to above by gas chromatography.

See the attached chromatography chart.

Cyclopentasiloxane and Hydrogenated polyisobutene are detected by gas chromatography . There are some minor peaks detected after the retention time of Cyclopentasiloxane. These peaks are assumed as low-molecular-weight MQ resin. We haven't detected the other prominent peaks.

5. Conclusion

These data suggest that the product doesn't contain Trifluoropropene and initial materials.


FID1 A, (04APR28¥SIG10904.D)
pA
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400
350
300
250
200
150
100
50
0
0
1
2
3
4
5
6
7
8
9
min
5.192
cyclopentasiloxane
D5
Hydrogenated
Polyisobutene
4.447
4.515
4.726
5.028
5.076
5.489
5.745
5.939
6.046
6.349
6.460
6.600
6.676
6.894
7.000
7.073
7.151
7.654
7.724
8.208
8.264
8.684

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: August 22, 2011

SUBJECT: Product Information Silica Silylate

Dow Corning. 2009. Product information: Dow Corning® VM-2270 Aerogel Fine Particles (Silica Silylate).

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Product Information
Personal Care

DOW CORNING

Dow Corning® VM-2270 Aerogel Fine Particles

FEATURES

- White free-flowing powder
- Capable of absorbing non-polar and polar oils
- Thickening agent for organic oils and silicone fluids

BENEFITS

- Superior oil and sebum absorption
- Highly efficient viscosity enhancement of oil phase
- Fragrance retention

INCI Name: Silica Silylate

APPLICATIONS

- AP/Deo
- Skin care
- Fragrance
- Hair care

TYPICAL PROPERTIES

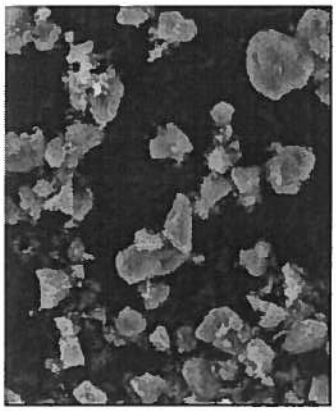
Specification Writers: These values are not intended for use in preparing specifications. Please contact your local Dow Corning sales office or your Global Dow Corning Connection before writing specifications on this product.

Property	Unit	Value
Appearance		White, free-flowing, powder
Bulk density	kg/m^3	40-100
Average particle size	microns	5-15
Surface area	m^2/g	600-800
Porosity	%	>90

DESCRIPTION

The *Dow Corning*® VM-2270 Aerogel Fine Particles are supplied as a white free flowing powder. The particles are completely hydrophobic providing a vehicle for thickening oil phase materials, reducing the volatility of many volatile fluids and the absorption of many lipophilic materials including sebum.

Figure 1: S.E.M of *Dow Corning* VM-2270 Aerogel Fine Particles.



HOW TO USE

It is recommended to first disperse the *Dow Corning* VM-2270 Aerogel Fine Particles into a low molecular weight silicone or organic fluid and then add this pre-mix to the formulation with high shear mixing to break up any agglomerated particles.

When making an emulsion with the *Dow Corning* VM-2270 Aerogel Fine Particles, incorporate the particles into the oil phase and mix with high shear to break up any agglomerate particles.

Premixing the oil phase is preferred over post addition of the particles after the emulsion is made.

Recommended use level is 0.5 to 5%.

HANDLING PRECAUTIONS

Product safety information required for safe use is not included. Before handling, read product and safety data sheets and container labels for safe use, physical and health hazard information. The material safety data sheet is available on the Dow Corning website at www.dowcorning.com. You can also obtain a copy from your local Dow Corning sales representative or Distributor or by calling your local Dow Corning Global Connection.

USABLE LIFE AND STORAGE

When stored at or below 40°C (104°F) in the original unopened containers, this product has a usable life of 24 months from the date of production

PACKAGING

This product is available in 10kg box.

Samples are available in 1 liter bottles.

LIMITATIONS

This product is neither tested nor represented as suitable for medical or pharmaceutical uses.

HEALTH AND ENVIRONMENTAL INFORMATION

To support Customers in their product safety needs, Dow Corning has an extensive Product Stewardship organization and a team of Product Safety and Regulatory Compliance (PS&RC) specialists available in each area.

For further information, please see our website, www.dowcorning.com or consult your local Dow Corning representative.

LIMITED WARRANTY INFORMATION – PLEASE READ CAREFULLY

The information contained herein is offered in good faith and is believed to be accurate. However, because conditions and methods of use of our products are beyond our control, this information should not be used in substitution for customer's tests to ensure that our products are safe, effective, and fully satisfactory for the intended end use. Suggestions of use shall not be taken as inducements to infringe any patent.

Dow Corning's sole warranty is that our products will meet the sales specifications in effect at the time of shipment.

Your exclusive remedy for breach of such warranty is limited to refund of purchase price or replacement of any product shown to be other than as warranted.

DOW CORNING SPECIFICALLY DISCLAIMS ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS FOR A PARTICULAR PURPOSE OR MERCHANTABILITY.

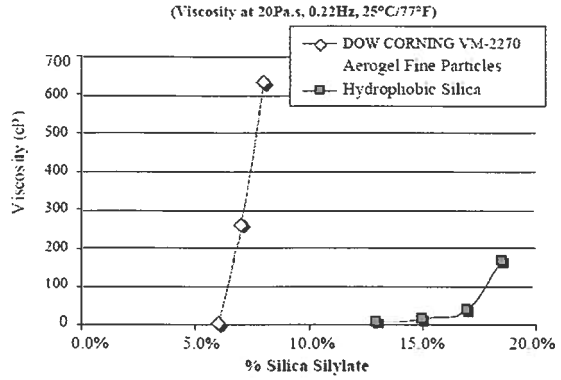
DOW CORNING DISCLAIMS LIABILITY FOR ANY INCIDENTAL OR CONSEQUENTIAL DAMAGES.

We help you invent the future. ™

www.dowcorning.com

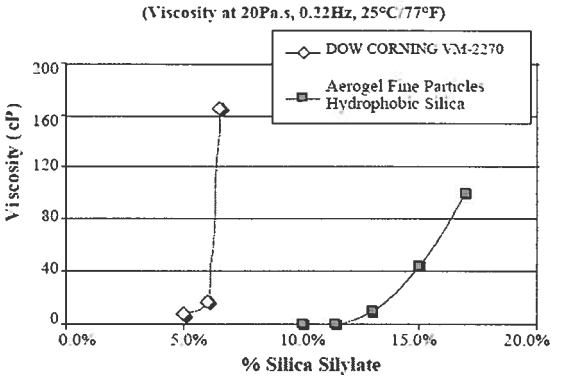
2009, April 01
Ref. No. 27-1215C-01

Figure 2: Thickening effect in mineral oil[1].



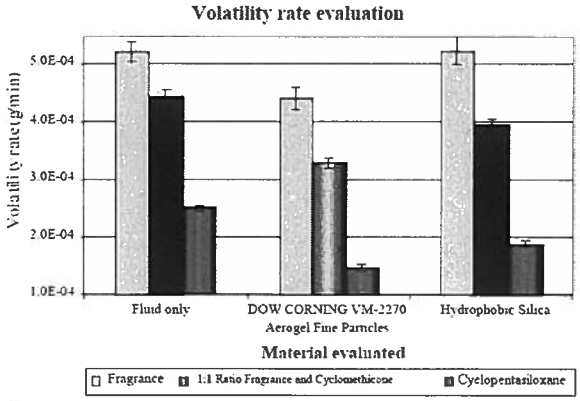
1. Data generated using Carrimed Rheometer

Figure 3: Thickening effect of Dimethicone (10cs)[1].



1. Data generated using Carrimed Rheometer

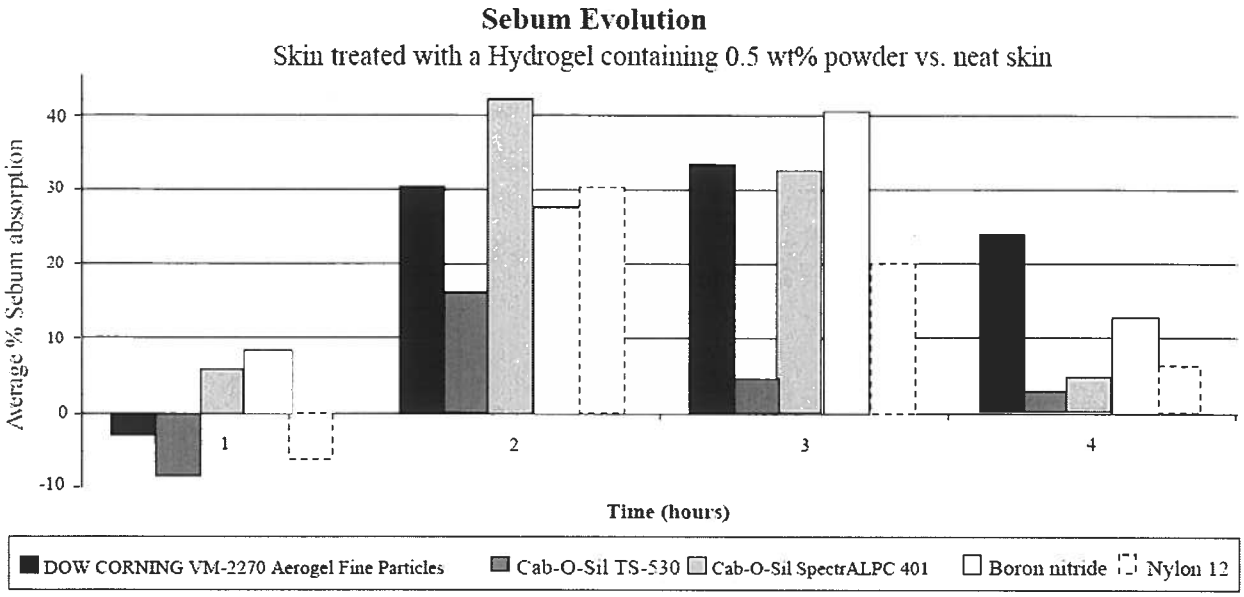
Figure 4: Volatility reduction evaluation[1].



(Results significant at 95% confidence level).

1. Weight loss measured at 20°C (68°F). 41% R.H. Fluids tested: XIAMETER® PMX-0245 Fluid and Fragrance Oil provided byGivaudan (Lot L400329). Cyclopentasiloxane

Figure 5: Sebum absorption[1].



1. Data generated using Sebumeter SM 810.

Table 1: Fluid absorption properties.

Ingredient	Absorption results (g fluid/g Aerogel)
Solvents	
Water	Not Compatible
Glycerin	Not Compatible
Esters	
Octyl palmitate	>15
Isopropyl myristate	>15
Oils	
Essential oil (lavender)	>10
Fragrance	7-10
Jojoba oil	8
Castor oil	6
Sunflower oil	>15
Mineral oil	>15
Retinyl palmitate	>10
Hydrocarbons	
Hydrogentate polyisobutylene	>10
Isododecane	>15
Silicones	
XIAMETER® PMX-0245 Cyclopentasiloxane	>15
Dow Corning ® 5562 Carbinol Fluid	8-9
XIAMETER® PMX-200 Silicone Fluid, 10 cSt	10

Table 2: Prototype formulations.

HYDROGEL

Ingredients	INCI Name	Weight %	Supplier
Carbomer gel (1% in water)	Carbomer	50.0	Noveon Inc.
Water		38.5	
Propylene glycol	Propylene glycol	5.0	
Dow Corning VM-2270 Aerogel Fine Particles	Silica Silylate	0.5	Dow Corning
XIAMETER® PMX-0345 Cyclosiloxane Blend	Cyclopentasiloxane (and) Cyclohexasiloxane	6.0	XIAMETER

Procedure:

a) Prepare the carbomer gel (1% water) and neutralize it with NaOH (10% solution).
b) Put the carbomer gel in a beaker, add water and mix (1200rpm) using the carbomer propeller.
c) Add propylene glycol and mix (1200rpm) until the batch becomes homogeneous.
d) In a separate vessel, add XIAMETER® PMX-0345 Cyclosiloxane Blend to the powder and mix.
e) When it is homogeneous, add the blend to the hydrogel and mix until complete homogenization.

ANTIPERSPIRANT

Ingredients	INCI Name	Weight %	Supplier
Dow Corning® 9040 Elastomer Blend	Cyclopentasiloxane (and) Dimethicone Crosspolymer	30.0	Dow Corning
XIAMETER® PMX-200 Silicone Fluid 10 cSt	Dimethicone	15.0	XIAMETER
XIAMETER® PMX-0245 Cyclopentasiloxane	Cyclopentasiloxane	29.0	XIAMETER
Aluminum chlorhydrate (reach 103)	Aluminum Chlorohydrate	25.0	Reheis Inc.
Dow Corning VM-2270 Aerogel Fine Particles	Silica Silylate	1.0	Dow Corning

Procedure:

a) Mix all ingredients together and mix for 5 minutes at 500rpm, using a strong mixer (carbomer mixer).

Synthetic Amorphous Silica
and Silicate Industry Association

Cosmetic Ingredient Review
1101 17th Street, NW, Suite 412
Washington, DC 20036

August 31, 2011

Dr. F. Alan Andersen, Director

Dear Dr. Andersen:

The Synthetic Amorphous Silica and Silicate Industry (SASSI) Association has reviewed the Tentative Safety Assessment (TSA) issued by CIR on July 6, 2011 for "Silica Silylate, Silica Dimethyl Silylate, Trimethylsiloxysilicate and Trifluoropropyldimethyl/Trimethylsiloxysilicate (as used in Cosmetics)", and would like to offer the following comments for consideration prior to the issuance of the Final Safety Report.

General comments:

1) As we discussed on August 16th, our February 24, 2011 letter to CIR (and the reference documents also provided at the same time) were not made available for review and consideration by the Expert Panel prior to the March 3-4 meeting or prior to the issuance of the July 7, 2011 TSA. It is imperative that before the publication of the Final Safety Report, a number of the key points we addressed in our letter need to be taken into consideration in light of the conclusions and recommendations in the TSA. We specifically refer the Expert Panel to "Specific comments 8, 9, 10, 11, and 12" in our February 24 letter and to the toxicity studies for HMDS- and PDMS-treated silicas summarized for all of the manufacturers' products in detail in the ECETOC JACC Report No. 51 – Synthetic Amorphous Silica, 2006, which was previously submitted to CIR.
2) Based on information that has been made available, we disagree with the Expert Panel's assessment "that no inhalation toxicity data were available."
3) Based on information that has been made available, we consider as not relevant the studies referenced by the Expert Panel in forming their conclusion that "Inhalation data show that the particles do reach the lungs in rats and induce granulomata formation. There is also necrosis or atrophy of the olfactory epithelium observed. There are currently no data available on which to base a finding of safe for use in products which may be inhaled."
4) Based on information that has been made available and the recommendations of CIR in Safety Assessment of Silica and Related Cosmetic Ingredients (Sept. 25, 2009), we do not believe the recommendation for a "13-week inhalation toxicity study that evaluates both the nasopharyngeal cavity and the lung, using the smallest particle size available for use in cosmetics" is warranted.

Specific comments:

1) For General Comments 2, 3 & 4: The ECETOC JACC No. 51 report includes surface-treated SAS, including Silica Silylate (treated with hexamethyldisilazane), Silica Dimethyl Silate (treated with dimethyldichlorosilane) and Silica Dimethicone Silylate (treated with polydimethylsiloxane). The report states: "The surface treatment does not change the solid properties e.g. particle size, dissolution kinetics of the inorganic polymer silicon dioxide (silica, SiO2). However, surface treatment does alter the physico-chemical properties, e.g. reduced moisture uptake." In the summary of the toxicological testing (Chapter 8 of the ECETOC report), information on surface-treated SAS is summarized under "hydrophobic SAS".
2) In response to General Comment 3, reference 60 is not relevant because the material causing the effects of concern contained crystalline silica (quartz).
1) In response to General Comment 4: With respect to particle size distribution see page 7 of "Safety Assessment of Silica and Related Cosmetic Ingredients (CIR: Sept. 25, 2009)": "**Particle Size and Form: Silica:** Amorphous Silicas are composed of very fine particles (average of 20 μm) which tend to aggregate loosely in the air (Byers and Gage 1961). Primary particles, or single particles, do not exist in isolation in fumed (pyrogenic) and precipitated silica; only in silica sol (colloidal). Aggregates assemble in chains (fumed) or clusters (precipitated and gel). Agglomerates are assemblies of aggregates, held together by strong physical adhesion forces and not in a dispersible nano size (< 100 nm) (ECETOC 2006; Gray and Muranko 2006)." As reference above, "surface treatment does not change the solid properties e.g. particle size…"

As I mentioned in our previous letter, we are open to discussing any opportunity to assist CIR in completing a comprehensive and accurate review of treated synthetic amorphous silica. Please contact me if the Expert Panel has any questions about our comments or to determine how we can further support the efforts of your organization.

We look forward to continuing our communication with your organization.

Sincerely yours,

David A. Pavlich
Association Manager
Synthetic Amorphous Silica and Silicate Industry
www.sassiassociation.org
440-897-8780

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: August 25, 2011

SUBJECT: Comments on Inhalation Exposure Studies Included in the Tentative Report on the Silylate Ingredients
Updated Concentration of Use Information Silica Dimethyl Silylate, Trimethylsiloxysilicate

At the June Panel meeting, the CIR Expert Panel was concerned with the potential of Silica Dimethyl Silylate to cause granulomas based on reference 60 cited in Table 4 of the report. Reference 60 in the Tentative Report on Silylates and Surface Modified Siloxysilicates As Used in Cosmetics is not an appropriate reference for this report and should be removed from the report. The title of the reference is: "Subchronic (13-week) inhalation of aerosols of "reaction products of dichlorodimethyl silane with silica" and Quartz in rats." Quartz is a form of crystalline silica which causes granulomas and silicosis, and it is not relevant to the ingredients included in this report which are surface-treated amorphous silica.

Reuzel et al. (1991) (a reference cited in the CIR report on Silica) compared the subchronic inhalation toxicity of three different amorphous silicas with quartz dust in rats. They concluded that the following were the most important differences in effects between quartz and the amorphous silicas:

> "Quartz, but not the amorphous silica, induced persistent granulomas very much resembling silicotic nodules.
> The adverse effects in the respiratory tract induced by the amorphous silica partly or completely regressed after exposure was ended, whereas most of the quartz-induced changes progressed."

Granulomas were not observed in rats exposed to the lowest concentration (1.3 mg/m^3) of an amorphous silica that caused granuloma-like lesions in some rats at 30 mg/m^3.

The discussion section of the CIR Silica report states that: "the Panel considered that any spray containing these solids should be formulated to minimize their inhalation potential", and concluded that "Silica, alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicates, hydrated silica, and sodium potassium aluminum silicate are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment." The discussion and conclusion of the CIR silylates report should be similar to that included in the CIR silica report.

The ECETOC (2006) report on Synthetic Amorphous Silica (SAS) (cited in the CIR report on silica, but not the CIR report on the silylate ingredients) includes surface-treated SAS including Silica Silylate (described by ECETOC as treated with hexamethyldisilazane), Silica Dimethyl Silate (described by ECETOC as treated with dimethyldichlorosilane) and Silica Dimethicone Silylate[1] (described by ECETOC as treated with polydimethylsiloxane). In the Identity section describing surface-treated SAS, ECETOC states: "The surface treatment does not change the solid properties e.g. particle size, dissolution kinetics of the inorganic polymer silicon dioxide (silica, SiO2). However, surface treatment does alter the physico-chemical properties, e.g. reduced moisture uptake." In the summary of toxicological testing (Chapter 8 of the ECETOC report), information on surface-treated SAS is summarized under "hydrophobic SAS".

Dr. Valerie Moise, Cabot Corporation has also provided the following information regarding surface-treated silica: "With regard to particle size, Cab-O-Sil TS-530 [Silica Silylate] and TS-720 [Silica Dimethicone Silylate] exist primarily as aggregates and agglomerates (i.e., not as their primary particles). The size is dependent upon the handling method as well as the measurement technique used. For the purposes of inhalation studies in rats, particle size is typically measured during the exposure period by cascade impactor or aerodynamic particle sizer. However, the sizes measured during these inhalation studies cannot be compared to typical workplace or consumer exposure, as the silica particles are administered using shear forces in order to break up the agglomerates into sizes that are respirable to the rats (i.e., between 1 micron and 4 microns as required in the OECD Guidelines for inhalation testing in rats). In these studies, the animals are exposed to very high dust levels relative to the surface of their lungs causing them to experience lung inflammation as a result of pulmonary overload and the inability to clear the large number of particles administered. This is considered a physical effect and not a direct toxic effect. During the animal studies with recovery periods, clearance was observed once the exposure ceased, and the particles were removed by the lymph nodes. After years of experience with inhalation tests in rats and gaining an understanding of the unique physical properties of synthetic amorphous silicas, we have learned that these studies are not relevant to typical workplace or consumer exposure. Hence, conducting another 13-week inhalation study (as suggested in the current CIR report) will not provide any additional useful information for risk assessment purposes.

Note that there are other studies that are missing from the CIR report including a 13-week study that was conducted on another silica silylate product. These studies are described in the ECETOC JACC Report No. 51 - Synthetic Amorphous Silica (2006) (http://www.ecetoc.org/jacc-reports; SAS is report 51 - Fill in details information and the link to download the full report will be sent to your e-mail

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[1]The ECETOC report defines Silica Dimethicone Silylate as Si-O-[$Si(CH_3)_2$-O-]$_{x=3-6(10)}$. Although Silica Dimethicone Silylate is an INCI name (25 uses reported to the VCRP) and some data on this ingredient e.g., trade name Cab-O-Sil TS-720 (incorrectly identified as Silica Dimethyl Silylate in the CIR report), are included in the silylate report, this ingredient is not currently listed as an ingredient in the CIR report on silylates.

address) , which is currently the most complete source of toxicology data on synthetic amorphous silicas.[2]

Also, chapter 8 contains more details on the repeated dose inhalation studies and their relevance to the consumer. Although the JACC Report was previously submitted to the CIR, the CIR did not include all of the studies and focuses mainly on the dimethyldichlorosilane-treated silicas (silica dimethyl silylate). Based on the incomplete nature of the CIR report and its lack of understanding of the studies presented, the CIR should not be used for decision-making or as a sole source of data on these surface treated silica products."

Additional Comments Table 4 CIR Tentative Report on the Silylate Ingredients

In Table 4 of the Silylate report under reference 59, it should be noted that particle size could not be measured because of electrostatic charge of the particles. It should also be stated that the LOAEL was based on histopathological findings in the lungs.

It should also be noted that rather than a negative control, reference 61 (the last study in Table 4) used a positive control. The positive control rats (n=120) were exposed to 45 mg/m^3 Aerosil (a trade name for amorphous silica).

References (from CIR silica report)

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) 2006. Synthetic Amorphous Silica (CAS No. 7631-86-9). JACC No. 51. Brussels. 237 pages.

Reuzel, P.G.J., J.P. Bruijntjes, V.J. Reron, and R.A. Woutersen. 1991. Subchronic inhalation toxicity of amorphous silica and quartz dust in rats. Fd. Chem. Toxic. 29:341-354.

Updated Concentration of Use Information

Use information for Silica Dimethyl Silylate and Trimethylsiloxysilicate has been updated. Please see the end of the table for details of the changes.

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[2]Comments from the Synthetic Amorphous Silica and Silicate Industry (SASSI) Association (submitted to CIR February 24, 2011) also suggested that the ECETOC report be used as source for studies on surface-treated SAS. For example, Table 36 of the ECETOC report includes inhalation studies of Silica Silylate including a 1 year study in monkeys identifying a NOAEL of 10 mg/m^3. As the studies in Table 36 are presented by trade names, Appendix B of the ECETOC report needs to be used to link the trade name to the treating agent.

Concentration of Use by FDA Product Category
Silica Dimethyl Silylate, Trimethylsiloxysilicate and
Trifluoropropyldimethyl/Trimethylsiloxysilicate

Ingredient	Product Category	Concentration of Use
Silica Dimethyl Silylate	Eyeliner	1-2%
Silica Dimethyl Silylate	Eye shadow	0.00003-3%
Silica Dimethyl Silylate	Eye lotion	0.03%
Silica Dimethyl Silylate	Mascara	0.0003-1%
Silica Dimethyl Silylate	Colognes and toilet waters	0.5%
Silica Dimethyl Silylate	Perfumes	3%
Silica Dimethyl Silylate	Powders (dusting and talcum)	4%
Silica Dimethyl Silylate	Other fragrance preparations	3%
Silica Dimethyl Silylate	Blushers (all types)	0.00003-3%
Silica Dimethyl Silylate	Face powders	0.02-2%
Silica Dimethyl Silylate	Foundations	0.3-6%
Silica Dimethyl Silylate	Lipstick	1-10%
Silica Dimethyl Silylate	Makeup bases	1%
Silica Dimethyl Silylate	Other makeup preparations	0.9-2%
Silica Dimethyl Silylate	Nail polish and enamel	2%
Silica Dimethyl Silylate	Other manicuring preparations	0.002%
Silica Dimethyl Silylate	Deodorants (underarm)[1]	0.002%
Silica Dimethyl Silylate	Other personal cleanliness products	0.0009-4%
Silica Dimethyl Silylate	Face and neck creams, lotions and powders	0.08-5%
Silica Dimethyl Silylate	Body and hand creams, lotions and powders	0.03-3%
Silica Dimethyl Silylate	Moisturizing creams, lotions and powders	1-2%

Silica Dimethyl Silylate	Night creams, lotions and powders	0.05-0.1%
Silica Dimethyl Silylate	Skin fresheners	0.1%
Silica Dimethyl Silylate	Other skin care preparations	0.02-0.2%
Silica Dimethyl Silylate	Suntan gels, creams and liquids	0.5%
Silica Dimethyl Silylate	Indoor tanning preparations	0.9%
Trifluoropropyldimethyl/ Trimethylsiloxysilicate	Eyeliner	20%
Trifluoropropyldimethyl/ Trimethylsiloxysilicate	Foundations	10%
Trifluoropropyldimethyl/ Trimethylsiloxysilicate	Suntan gels, creams and liquids	2%
Trimethylsiloxysilicate	Eyebrow pencil	6-12%
Trimethylsiloxysilicate	Eyeliner	4-30%
Trimethylsiloxysilicate	Eye shadow	1-20%
Trimethylsiloxysilicate	Eye lotion	0.4-5%
Trimethylsiloxysilicate	Mascara	4-25%
Trimethylsiloxysilicate	Other eye makeup preparations	7%
Trimethylsiloxysilicate	Powders (dusting and talcum)	0.0001%
Trimethylsiloxysilicate	Hair straighteners	5%
Trimethylsiloxysilicate	Hair dyes and colors (all types requiring caution statement and patch test)	0.1%
Trimethylsiloxysilicate	Blushers (all types)[2]	0.7-19%
Trimethylsiloxysilicate	Face powders	3-8%
Trimethylsiloxysilicate	Foundations	0.5-13%
Trimethylsiloxysilicate	Leg and body paints	4%
Trimethylsiloxysilicate	Lipstick	2-30%
Trimethylsiloxysilicate	Makeup bases	2%
Trimethylsiloxysilicate	Other makeup preparations	3-20%

Trimethylsiloxysilicate	Basecoats and undercoats (manicuring preparations)	0.02%
Trimethylsiloxysilicate	Nail polish and enamel	0.02-0.1%
Trimethylsiloxysilicate	Bath soaps and detergents	0.002-2%
Trimethylsiloxysilicate	Other shaving preparations	0.7%
Trimethylsiloxysilicate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.5%
Trimethylsiloxysilicate	Face and neck creams, lotions and powders	0.4-2%
Trimethylsiloxysilicate	Body and hand creams, lotions and powders	0.1-3%
Trimethylsiloxysilicate	Body and hand sprays	0.4%
Trimethylsiloxysilicate	Moisturizing creams, lotions and powders	0.6%
Trimethylsiloxysilicate	Night creams, lotions and powders	0.4%
Trimethylsiloxysilicate	Other skin care preparations	0.2-13%
Trimethylsiloxysilicate	Suntan gels, creams and liquids	0.005-10%
Trimethylsiloxysilicate	Indoor tanning preparations	0.08-0.7%

[1]0.002% in a non-spray deodorant
[2]19% in a cream blush stick

Information collected in 2010
Table prepared July 21, 2010
Updated August 22, 2011 (Silica Dimethyl Silylate: deodorants 2% product no longer made; 0.002% deodorant product is not a spray product; Trimethylsiloxysilicate: blushers highest concentration increased to 19%, footnote added; face powders highest concentration reduced to 8%)

Cosmetic Use: Silylates

According to the Voluntary Cosmetic Registration Program (VCRP) administered by the Food and Drug Administration (FDA), the total number of uses of silica dimethyl silylate was 734 (592 leave-on and 142 rinse-off products).[1] A survey conducted by the Personal Care Products Council (Council) found that silica dimethyl silylate was used at 0.00003% – 10% in leave-on products (highest concentration in lipsticks) and 0.0003% - 4% in rinse-off products (highest concentration in personal cleanliness products; Table 3).[2] There were 633 uses reported of trimethylsiloxysilicate at 0.0001% - 30% in leave-on products (highest in eyeliner and lipsticks) and 0.002% - 5% in rinse-off products (highest in hair straighteners). There were 245 used reported of silica silylate (244 in leave-on and 1 rinse-off product) at 0.2% - 25 in leave-on products.[3] There were no uses reported of trifluoropropyldimethyl/trimetylsiloxysilicate by FDA but the Council reported use at 2% – 20% in leave-on products (highest in eyeliner).

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[1-3]

	Silica silylate		Silica dimethyl silylate		Trimethylsiloxysilicate		Trifluoropropyldimethyl/ trimethylsiloxysilicate	
	# of Uses	Concentration (%)	# of Uses	Concentration (%)	# of Uses	Concentration (%)	# of Uses	Concentration (%)
Exposure Type								
Eye	80	1-6	45	0.00003-3	255	0.4-30	NR	20
Incidental ingestion	96	2-24	281	1-10	30	2-30	NR	NR
Incidental inhalation-sprays	1	NR	35	0.002-3	17	0.005-10*	NR	2
Incidental inhalation-powders	6	0.2-4	17	0.02-4	51	0.0001-8		NR
Dermal contact	126	0.2-7	313	0.00003-6	501	0.0001-30	NR	2-20
Deodorant (underarm)	NR	NR	27	0.002	NR	NR	NR	NR
Hair – non coloring	NR	17-25	2	NR	13	5	NR	NR
Hair - coloring	NR	NR	130	NR	6	0.1	NR	NR
Nail	21	10	5	0.002-2	43	0.02-0.1	NR	NR
Mucous Membrane	97	2-24	285	0.0009-10	30	0.002-30	NR	NR
Baby products	NR	NR	1	NR	NR	NR	NR	NR
Duration of Use								
Leave-on	244	0.2-25	592	0.00003-10	611	0.0001-30	NR	2-20
Rinse-off	1	NR	142	0.0003-4	22	0.002-5	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR		NR
Totals/conc. range	**245**	**0.2-25**	**734**	**0.00003-10**	**633**	**0.0001-30**	NR	**2-20**

NR = not reported; Totals = rinse-off + leave-on product+diluted for bath uses.
* 0.4% in a body and hand skin care product.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

1. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2011. Washington, DC: FDA.

2. Personal Care Product Council. 8-25-2011. Concentration of Use by FDA Product Category Silica Dimethyl Silylate, Trimethylsiloxysilicate and Trifluoropropyldimethyl/Trimethylsiloxysilicate. 3 pages.

3. Personal Care Products Council. 3-15-2011. Concentration of Use by FDA Product Category: Silica Silylate. 2 pages.

Synthetic Amorphous Silica (CAS No. 7631-86-9)

JACC No. 51

ISSN-0773-6339-51
Brussels, September 2006

collected and analysed for the monomer silica content. During the following three days no significant changes of the renal silica secretion were seen after administration of Aerosil. With precipitated silica in 5/6 persons the renal SiO_2 secretion was increased by 7 to 23 mg. In 1/6 persons it was decreased by 26 mg. In 5/6 persons the average daily precipitated silica secretion of the following 3 days was increased by 4 to 20 mg and slightly decreased in 1/6 persons. The changes in silica excretions were considered by the authors to be within the range of normal physiological variation, and there was little indication of absorption across the gut wall (Degussa, 1966a; Langendorf and Lang, 1967).

The short-term safety and efficacy of Syloid HC gel was studied in 6 human adults (3 men, 3 women; aged 20 - 51 y) with primary type II hyper-lipoproteinaemia. For 3 weeks, Syloid HC was administered with the morning and evening meal, starting with an oral dose of 1 g/d that was increased by 1 g/d daily, up to a final dose of 16 g/d. Syloid HC was not absorbed significantly from the intestine. No marked adverse side effects were observed. The substance did not markedly enhance bile acid excretion (Grace, 1982).

7.1.3 Studies in animals

Inhalation

An inhalation study was conducted in rats, including two pyrogenic SASs [a] (hydrophilic Aerosil 200 and hydrophobic Aerosil R974) and precipitated, hydrophilic Sipernat 22S. Rats were exposed (6 h/d, 5 d/wk) to SAS for 13 weeks to concentrations of 1.3, 5.9 or 31 (Aerosil 200) or 35 (Aerosil R974 and Sipernat 22S) mg SiO_2/m^3 with recovery up to 52 weeks. Small amounts of SAS, compared to the administered dose, could be detected in lungs at the end of the exposure period (average 0.2 mg) in all animals of the high dose group. One male exposed to 31 mg/m^3 showed a small amount of silica in the regional lymph nodes. During the recovery period no SAS could be detected in the lungs or nodes of any animal (Degussa, 1987; Reuzel *et al,* 1991).

Rats were exposed by inhalation for 5 hours to 55 mg/m^3 precipitated SAS (FK700). The mean retention value (20 h later) was 0.138 mg SiO_2/lung. The average silica content of the lungs was 1.022 mg after 4 months of exposure, and 3.443 mg after 12 months. The corresponding values for the mediastinal lymph nodes were 0.033 mg after 4 months, 0.052 mg after 5 months and 0.069 mg after 12 months. The average silica content of the lungs was 0.457 mg (elimination 87%) 5 months after exposure (Degussa, 1968b). This indicates that there was no significant elimination of SAS via the mediastinal lymph nodes, such as that observed with quartz.

[a] The various SASs studied are listed in Appendix B. The physical and chemical properties are discussed in Section 2.3.

Table 30: Acute inhalation toxicity of hydrophobic SAS to rats

Type/ Product name	Strain, number and sex	Surface area [a] (m^2/g)	Particle size MMAD [b] (µm)	Exposure duration (h), regime [c]	Concentration (mg/m^3)	LC_{50} (mg/m^3), remark	Reference	CoR [d]
Pyrogenic								
Aerosil R809	Wistar, 5 M, 5 F	80	1.4 - 1.8	4	1,094, 2,863, 3,730, 5,382	2,863 - 3,730	Degussa, 1984a	2b
Aerosil R972	Strain not specified, 5 M, 5 F	130	0.15	1	2,280	> 2,280	Cabot, 1982a	2b
Aerosil R974	Wistar, 5 M, 5 F	200	< 5 (56%) ≥ 7.7 (44%)	4	477	> 477	Degussa, 1983c	2b
Cab-O-Sil N70TS	SD, 5 M, 5 F	200	0.36	4	0 (control), 4,900	< 4,900 All died at 4,900	Cabot, 1981d	2b
Cab-O-Sil N70TS	SD, 5 M, 5 F	200	0.54	4	0 (control), 2,190	< 2,190 All died at 2,190	Cabot, 1981e	2b
Cab-O-Sil N70TS	SD, 5 M, 5 F	200	0.48	1	0 (control), 1,260, 2,830, 6,280	1,260 - 2,830	Cabot, 1982b,c	2b
Cab-O-Sil silane-treated [e]	Wistar, 10 M [f]	Not specified	Not specified	6	250 (nominal)	> 250	Cabot, 1963b	2c
Cab-O-Sil ST22 [g]	Albino rat, strain not specified, 10 M	Not specified	Not specified	1, not stated	670, 690, 710, 1,540, 3,150	> 3,150	Cabot, 1970b	3a

Table 30: Acute inhalation toxicity of hydrophobic SAS to rats (cont'd)

Type/ Product name	Strain, number and sex	Surface area (m^2/g)	Particle size MMAD (µm)	Exposure duration (h), regime	Concentration (mg/m^3)	LC_{50} (mg/m^3), remark	Reference	CoR
Pyrogenic (cont'd)								
Cab-O-Sil TS610	Wistar, 5 M, 5 F	130	1.175 -1.275	4	210, 540, 2,100	450	Cabot, 1994a	1b
Cab-O-Sil TS530	Wistar, 5 M, 5 F	300	0.95 - 2.15	4	90, 840	90 - 0.840	Cabot, 1994b	1b
HDK SKS130	SD, 5 M, 5 F	130	< 0.2	4	350, 770, 2,530, 5,300	1,650	Wacker, 1996b	1a
HDK SKS130	SD, 5 M, 5 F	130	7.2 - 7.7	4, nose-only	900, 2,200 [h]	> 2,200 [h]	Wacker, 1996c	1a
HDK SKS300	SD, 5 M, 5 F	300	< 0.1	4	90, 350, 5,000	90	Wacker, 1996d	1a
HDK SKS300	SD, 5 M, 5 F	300	7 - 7.1	4, nose-only	400, 600	500	Wacker, 1996e	1a
HDK SKS300 VI	SD, 5 M, 5 F	300	< 0.4	4	80, 340, 1,200, 5,000	800	Wacker, 1996f	1a
HDK SKS300 VI	SD, 5 M, 5 F	300	6.3 - 7.7	4, nose-only	400, 700, 2,000	600	Wacker, 1996g	1a
J-DCA TX104	SD, 3 M, 3 F	300	1 - 5 (83%) 5 - 100 (17%)	4	120, 400, 1,370, 3,360	660	Dow Corning, 1972	2b

[a] Referring to the surface of the hydrophilic base silica (BET)
[b] Mass median aerodynamic diameter (method: cascade impactor)
[c] Whole-body, unless stated otherwise
[d] Code of reliability (Appendix A)
[e] Treating agent not stated; actual identity of this product remains unclear
[f] Same test and results in mice (Swiss, 10 M) and guinea pigs (English short hair, 10 M)
[g] Aminopropylsilane-treated pyrogenic SAS
[h] 4/10 died at this (maximal attainable) concentration

The inhalation toxicity of Aerosil R974 was studied in Wistar rats by exposing them to the maximum attainable concentration of 477 mg/m^3 for 4 hours, followed by 14 days observation. Exposure resulted in a transient loss of body weight during the first 2 days of the observation period. Thereafter the animals gained weight in a normal way. No mortality occurred during the test. No abnormalities were found during gross pathological examination (Degussa, 1983c).

Degussa (1964a) and Cabot (1982d) reported that the SASs tested had completely occluded some of the smaller bronchioles at 40 to 80 (Aerosil R972) and 2,190 mg/m^3 (N70TS). Additionally, extravasation of blood was observed. These effects were seen as an indication of suffocation (Degussa, 1964a). The adverse effects in these studies appear to be primarily due to the physical presence of the test material rather than to a direct toxic effect of the substance.

Rats, mice and guinea pigs exposed to SAS (silane-treated Cab-O-Sil) at a concentration of 250 mg/m^3 for 6 hours showed preening in all species, hunching in rats, and occasional prostration among mice and rats; the response of the guinea pigs was not remarkable. No deaths were observed among mice. One guinea pig died after 250 minutes of exposure and one rat died 1 day after exposure. These deaths were considered coincidental to the inhalation of SAS. Only the occurrence of consolidation, seen in the lungs of 2 of 9 guinea pigs, was considered to be associated with an effect of the compound. No significant gross pathological changes were noted in surviving animals that could be attributed to inhalation of SAS (Cabot, 1963b).

8.1.4 Summary and evaluation

Numerous acute inhalation toxicity studies have been conducted on both hydrophilic and hydrophobic SAS. For hydrophilic SASs, LC_{50} values are higher than the highest technically achievable concentrations. The mortality observed with hydrophobic SAS is due to suffocation associated with the extremely high particle numbers administered and not with any intrinsic toxicity of the SAS tested.

In all of the acute inhalation tests where particle size data are available, the silica tested differs significantly from the commercial SAS product, based on particle size distribution. This is due to the experimental design that causes a significant reduction of the particle size, so that nearly 100% of the particle fraction has a MMAD below 10 µm (respirable, alveolar particle fraction). It is the alveolar fraction that is responsible for the observed adverse effects, including suffocation and lung overload due to poor dust clearance mechanisms.

In contrast to the particle size distribution of SASs used in acute inhalation animal tests, only a minor fraction (less than 1%) of commercially available SAS types has been measured to be respirable (alveolar fraction < 10 µm MMAD), using test method EN/DIN 481 (Stintz and

Table 36: Toxicity of hydrophobic pyrogenic SAS following repeated inhalation

Type/ Product name	Species, strain	Number of animals/ group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Cab-O-Sil N70TS	Rat, CD	40 M, 40 F 20/sex, control	6 h/d, 5 d/wk, 4 wk	0, 60 on d 1, 30 thereafter	Deaths after 1 d at 60 mg/m^3 due to acute pulmonary haemorrhage with bronchiolar plugs. Active interstitial/ alveolar inflammation occurred and changed from diffuse reactions to more localised consolidative lesions. During post exposure, active inflammation less prominent, but some fibrosis and collagen apparent in the interstitium	Cabot, 1983	3b
Aerosil R974	Rat, Wistar	10 M, 10 F	6 h/d, 5 d/wk, 2 wk	0, 31, 87, 209	Signs of respiratory distress in all test groups. Body weight gain and food consumption reduced at 87 and 209 mg/m^3. No adverse change in haematological parameters. Changed liver and kidney weights at 87 and 209 mg/m^3, not associated with histopathological changes. Concentration-related increase in absolute/relative lung weight. Lungs of several animals/all groups pale, spotted, swollen and spongy, and occasional small haemorrhages. Lungs of animals in all test groups showed increased cellularity, accumulation of alveolar macrophages, alveolar oedema and early granulomata. NOAEL < 31 mg/m^3.	Degussa, 1986c	1d
Aerosil R974	Rat, Wistar	70 M, 70 F	6 h/d, 5 d/wk, 13 wk	34.7	Lung collagen content increased immediately after exposure, and did not return to control levels during 52 wk recovery. Granuloma-like lesions, alveolar macrophage accumulation, cellular debris, and increased septal cellularity occurred at varying times post exposure	Degussa, 1987; Reuzel *et al,* 1991	1b

Table 36: Inhalation toxicity of hydrophobic SAS following repeated inhalation (cont'd)

Type/ Product name	Species, strain	Number of animals/ group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
HDK SKS300	Rat, Wistar	10 M, 10 F	6 h/d, 5 d/wk, 13 wk	0, 0.51, 2.05, 10.01	Most effects only observed in high dose group. Increase in aspartate-amino-transferase level and alkaline phosphatase (M). Significant increase in absolute/relative weight of lungs and tracheobronchial lymph nodes. Lungs with red appearance, white spot(s) on the lungs (F). Accumulation of alveolar macrophages with few polymorphonuclear cells, accompanied by bronchiolar-alveolar epithelial hyperplasia and interstitial inflammatory cell infiltrates in lungs. Lung draining mediastinal lymph nodes showed increased histiocytosis and macrophage aggregates in paracortex and/or germinal centres. No indication of increased birefringence, typical for interstitial fibrosis. Clear recovery of all effects. NOEL = 0.51 mg/m^3	Wacker, 1998a,b	1a
J-DCA TX104	Rat, not stated	M, number not stated	6 h/d, 5 d/wk, 12 months	0, 10, 50, 150	10 mg/m^3 had no effect. 50 mg/m^3 and 150 mg/m^3 produced white foci on lung surfaces and collections of foamy macrophages within the alveoli. Peribronchial lymph nodes enlarged	Dow Corning, 1972	4a
J-DCA TX104	Monkey, Cynomolgus	M, number not stated	6 h/d, 5 d/wk, 12 months	0, 10, 50, 150	10 mg/m^3 had no effect. 50 mg/m^3 and 150 mg/m^3 produced interstitial fibrosis, which did not resolve or progress during recovery. Peribronchial lymph nodes enlarged	Dow Corning, 1972	4a

CD rats were exposed to Cab-O-Sil N70TS (also known as TS720) at a concentration of 0 or 30 mg SiO_2/m^3 for 4 weeks. Initial exposure was to 60 mg/m^3, but after one day 9 male rats died from "acute pulmonary haemorrhage accompanied by bronchiolar plugs with emphysema", and the concentration was lowered to 30 mg/m^3. The aerosol particles had a mean MMAD from 0.23 to 0.37 µm. Animals were killed after 1, 2 or 4 weeks of exposure. Two additional groups of rats were killed 6 and 12 weeks after exposure. SAS caused an active interstitial/alveolar inflammation, which changed from a diffuse reaction to more localised lesions. During recovery, active inflammation became less prominent, but some fibrosis and collagen proliferation was apparent in the interstitium (Cabot, 1983). The value of the Cabot study is limited because of methodological deficiencies, as follows. The proportion of the chronic pulmonary lesions that may have been due to the initial severe injury relative to those induced by the subsequent lower dose level (60 mg/m^3 compared to 30 mg/m^3) cannot be determined from the data. The methods used to generate the SAS aerosol were not state-of-the art. The MMAD was very small, ranging from 0.23 to 0.37 µm. This is not in accordance with OECD guidelines of MMAD that prescribe a diameter of 1 to 4 µm for respirable dust. The techniques used for tissue preservation were not optimal and could have generated artefacts, while tissue sampling was not uniform. Furthermore, the authors made several claims that were not supported by the histological techniques used. Finally, some of the control animals also exhibited lung lesions.

Wistar rats were exposed to hydrophobic, pyrogenic SAS (Aerosil R974) at concentrations of 0 (control), or 34.7 mg SiO2/m3 for 13 weeks. Additional animals were exposed to crystalline silica (quartz) at 58.5 mg/m^3. The MMAD was not determined, but there was a wide range for the geometric agglomerate/aggregate size distribution (1 - 120 µm). Animals were killed immediately after the exposure and at 13, 26, 39 and 52 weeks post exposure. In males, the silicon content of lungs and tracheobronchial lymph nodes was approximately 1.1 mg (2.35 mg SiO_2) immediately after exposure, declined at 13 weeks to 0.4 mg (0.86 mg SiO_2), increased again at 26 weeks to 1.1 mg (2.35 mg SiO_2) (no explanation given by authors), and became undetectable by 39 weeks of recovery. In females, the silicon content of lungs and lymph nodes was approximately 0.7 mg (1.50 mg SiO_2) immediately after exposure and then declined steadily to below detection by 39 weeks (silicon content data read from Figure 3 of publication). In both males and females, lung collagen content was statistically increased immediately after exposure; both controls and exposed animals still showed elevated levels (≈ 10%) by 52 weeks post exposure. In males, exposure to Aerosil R974 caused granuloma-like lesions, alveolar macrophage accumulation, and increased septal cellularity with recovery at 26, 52, and 52 weeks post exposure, respectively. In females, exposure to SAS caused granuloma-like lesions, alveolar macrophage accumulation, cellular debris and increased septal cellularity, all of which returned to normal after 26, 26, 13 and 52 weeks of recovery, respectively (Reuzel *et al,* 1991).

Wistar rats were exposed to HDK SKS300 at concentrations of 0, 0.51, 2.05 or 10.01 mg SiO2/m^3 for 13 weeks. The mean MMAD was 2.8, 3.62 and 4.47 µm, respectively. At

10.01 mg SiO2/m^3, statistically significant increases were seen in total protein, LDH and NAG in lung lavage fluid. Additionally significant increases were noted in total cell number and absolute numbers of neutrophils, macrophages/monocytes and lymphocytes. These increases were reflected in a statistically significant increase in the relative number of neutrophils with a concomitant decrease in the relative number of macrophages/monocytes. At 2.05 mg SiO2/m^3, changes were limited to an increased relative number of neutrophils with a concomitant decrease in the relative number of macrophages/monocytes, without influencing absolute cell numbers. No such changes were observed in animals of the low concentration group (0.51 mg/m^3) or at the end of the recovery period in all groups. Silica (measured as Si) was found in the lungs of all exposed animals in a concentration-related way; it was present in the tracheobronchial lymph nodes of animals exposed to 10.01 mg SiO2/m^3. By the end of the 13-week recovery period, silicon could still be detected in lungs and tracheobronchial lymph nodes of animals exposed to 10.01 mg SiO2/m^3. The silicon level in the lungs was decreased and the level in the lymph nodes increased, compared to the levels measured immediately after exposure (Wacker, 1998b). It is interesting to note that the incidence and severity of the histopathological changes observed in the lymph nodes of animals in the high concentration group had diminished (Wacker, 1998a).

Rats (strain not provided) and Cynomolgus monkeys (*Macaca fascicularis*) were exposed to J-DCA TX104 at concentrations of 0, 10, 50, or 150 mg/m^3 for up to 12 months. Animals were killed during the exposure (rats only at 2 weeks, 1, 3, or 6 months), at termination of exposure (both rats and monkeys at 12 months), or post exposure (rats at 14 months; monkeys at 14 or 24 months). In rats, mortality was dose related: 8% (control), 12% (10 mg/m^3), 26% (50 mg/m^3) and 33% (150 mg/m^3). In the surviving rats, 10 mg/m^3 had no effect, and 50 mg/m^3 and 150 mg/m^3 produced collections of foamy macrophages within the alveoli. In monkeys, 10 mg/m^3 had no effect, and 50 mg/m^3 and 150 mg/m^3 produced interstitial fibrosis, which did not resolve or progress during the recovery period (Dow Corning, 1972).

Summary: lowest-observed adverse effect levels

The effects of chronic inhalation of pyrogenic, precipitated, gel and sol SAS have been evaluated in mice, rats, guinea pigs, rabbits and monkeys exposed to concentrations ranging from 0.5 to 150 mg SiO_2/m^3. Although the value of some studies is limited, SAS exposure caused macrophage accumulation, reticulin fibre formation and nodule formation. Table 37 lists those subchronic and chronic inhalation studies that provide lowest-observed adverse effect levels (LOAELs). When available, NOAELs or NOELs were in the range of 0.5 to 10 mg/m^3. The difference in values may be explained by different particle size, and therefore the number of particles administered per unit dose. In general, as particle size decreases so does the NOAEL/LOAEL.

Table 37: Lowest-Observed Adverse Effect Levels (LOAELs) for SAS

Type/ Product name	LOAEL (mg/m^3)	Reference
Hydrophilic		
Pyrogenic		
Aerosil 200	50	Johnston *et al,* 2000
Aerosil 200	1.3	Reuzel *et al,* 1991
Cab-O-Sil	6.9	Groth *et al,* 1981
Cab-O-Sil M5	1.39	Arts and Kuper, 2003a
Dow Corning Silica	53	Schepers *et al,* 1957a,b,c
Precipitated		
Hi-Sil	6.9	Groth *et al,* 1981
Hi-Sil 233	126	Schepers, 1981
Precipitated	15	Schepers, 1962
Sipernat 22S	34.9	Reuzel *et al,* 1991
Zeosil 45	5.39	Arts *et al*, 2003
Gel		
Syloid 74	5.13	Arts and Kuper, 2003b
Hydrophobic		
Pyrogenic		
Aerosil R974	31	Reuzel *et al*, 1991
HDK SKS300	2.05	Wacker, 1998a,b
J-DCA TX104	50	Dow Corning, 1972

It is important to note that some of the studies are deficient in several aspects (see text above).

Also, importantly, the effects reported in the various other studies may not necessarily be adverse. The indices used by the investigators to assess the effects of silica exposure are established markers of inflammation and injury. However, what is not readily apparent is the functional or biological significance of the reported effects. Phrases such as “toxic effects” have been used without considering toxic significance. The importance of making this distinction is seen in the resolution of lung injury during recovery periods. For example, Reuzel *et al* (1991) reported that rats exposed to 1.3 mg/m^3 exhibited increases in lung collagen content and histological lesions, which resolved during the post exposure observation period. The inclusion of a post exposure

Degussa. 1981. Sub-chronic (13-week) oral toxicity study with Sipernat 22 in rats. Unpublished report V 81.268/201741 by Til HP, Hollanders VMH and Beems RB, CIVO Institutes TNO, Zeist NL. Degussa, Hanau, Germany.

Degussa. 1983a. Acute inhalation toxicity study of Aerosil 200 in rats. Unpublished report V 83.142/221216 by Appelman LM and Reuzel PGJ, CIVO Institutes TNO, Zeist, Netherlands. Degussa, Frankfurt am Main, Germany.

Degussa. 1983b. Acute inhalation toxicity study of Sipernat 22S in rats. Unpublished report V 83.111/221216 by Appelman LM and Reuzel PGJ, CIVO Institutes TNO, Zeist, Netherlands. Degussa, Hanau, Germany.

Degussa. 1983c. Acute inhalation toxicity study of Aerosil R974 in rats. Unpublished report V 83.112/221216 by Appelman LM, CIVO Institutes TNO, Zeist Netherlands. Degussa, Hanau, Germany.

Degussa. 1983d. Bacterial mutagenicity test on a toluene extract from Aerosil R972. Unpublished report. Oesch F, Pharmakologisches Institut der Universität, Mainz, Germany. Degussa, Frankfurt am Main, Germany.

Degussa. 1984a. Acute inhalation toxicity study of Aerosil R809 in rats. Unpublished report V 84.227/240385 by Viljeer JW, CIVO Institutes TNO, Zeist Netherlands. Degussa, Hanau, Germany.

Degussa. 1984b. Zur Bedeutung und Existenz von Primärteilchen bei hochdispersen Stoffen. Ferch H, Seibold K. Schriftenreihe Pigmente Nummer 60. Degussa, Frankfurt am Main, Germany.

Degussa. 1986a. A sub-acute (14-day) inhalation toxicity study of Aerosil 200 in rats. Unpublished report V 86.284/221216 by Reuzel PGJ and Woutersen RA, CIVO Institutes TNO, Zeist, Netherlands. Degussa, Frankfurt am Main, Germany.

Degussa. 1986b. A sub-acute (14-day) inhalation toxicity study of Sipernat 22S in rats. Unpublished report V 86.287/221216 by Reuzel PGJ and Woutersen RA, CIVO Institutes TNO, Zeist, Netherlands. Degussa, Frankfurt am Main, Germany.

Degussa. 1986c. A sub-acute (14-day) inhalation toxicity study of Aerosil R974 in rats. Unpublished report V 86.285/221216 by Reuzel PGJ and Woutersen RA, CIVO Institutes TNO, Zeist, Netherlands. Degussa, Frankfurt am Main, Germany.

Degussa. 1987. Sub-chronic (13-week) inhalation toxicity study of aerosols of Aerosil 200, Aerosil R974, Sipernat 22S and quartz in rats. Unpublished report and tables V 86.347/240718 by Reuzel PGJ, Woutersen RA and Bruyntjes JP, CIVO Institutes TNO, Zeist, Netherlands. Degussa, Frankfurt am Main, Germany.

Degussa. 1988. Silicosis – caused by amorphous silica? Schriftenreihe Pigmente 76 (Technical Bulletin Pigments 76). Degussa, Frankfurt am Main, Germany.

Degussa. 1990. Sident 9, acute toxicity, testing the acute toxicity after single oral administration in rats. Unpublished report, study 878894 by Zechel HJ and Berthold K. ASTA Pharma, Bielefeld, Germany. Degussa, Hanau, Germany.

Degussa. 1991a. Fällungskieselsäuren und Silikate, Herstellung, Eigenschaften und Anwendungen. Degussa, Frankfurt am Main, Germany.

Degussa. 1991b. Sident 9, acute toxicity, testing the primary irritation/corrosion after single application to the skin of the rabbit (patch test). Unpublished report, study 878905 by Berthold K, Zechel HJ, Piening B, Fichtner E. ASTA Pharma, Bielefeld, Germany. Degussa, Hanau, Germany.

Degussa. 1991c. Sident 9, acute toxicity, testing the primary irritation after single application to the eye of the rabbit. Unpublished report, study 878916 by Berthold K, Zechel HJ, Piening B, Fichtner E. ASTA Pharma, Bielefeld, Germany. Degussa, Hanau, Germany.

Degussa. 1992a. The acute toxicity of Aerosil 200 to *Daphnia magna* (OECD Guideline No. 202, 24 h). Unpublished report IMW-R 92/006 by Hooftman RN and Van Drongelen-Sevenhuijsen D, TNO Environmental and Energy Research, Delft, Netherlands. Degussa, Wolfgang, Germany.

Degussa. 1992b. The acute toxicity of Aerosil R974 to *Daphnia magna* (OECD Guideline no. 202, 24 h). Unpublished report IMW-R 92/027 by Hooftman RN and Van Drongelen-Sevenhuijsen D, TNO Environmental and Energy Research, Delft, Netherlands. Degussa, Wolfgang, Germany.

Degussa. 1992c. Acute toxicity test with Ultrasil VN 3 and *Daphnia magna* (OECD Guideline No. 202, 24 h). Unpublished report IMW-R 92/271 by Hooftman RN and Van Drongelen-Sevenhuijsen D, TNO Environmental and Energy Research, Delft, Netherlands. Degussa, Wolfgang, Germany.

Degussa. 1992d. The acute toxicity of Aerosil 200 to *Brachydanio rerio* (OECD Guideline No. 203, 96 h). Unpublished report IMW-R 92/007 by Hooftman RN and Van Drongelen-

Sevenhuijsen D, TNO Environmental and Energy Research, Delft, Netherlands. Degussa, Wolfgang, Germany.

Degussa. 1992e. The acute toxicity of Aerosil R974 to *Brachydanio rerio* (OECD Guideline No. 203, 96 h). Unpublished report IMW-R 92/028 by Hooftman RN and Van Drongelen-Sevenhuijsen D, TNO Environmental and Energy Research, Delft, Netherlands. Degussa, Wolfgang, Germany.

Degussa. 1992f. Acute toxicity with Ultrasil VN 3 and *Brachydanio rerio* (OECD Guideline No. 203, 96 h). Unpublished report IMW-R 92/272 by Hooftman RN and Van Drongelen-Sevenhuijsen D, TNO Environmental and Energy Research, Delft, Netherlands. Degussa, Wolfgang, Hanau.

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DFG. 2004. Allgemeiner Staubgrenzwert. In MAK- und BAT-Werte-Liste 2004, Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte. Mitteilung 40. Deutsche Forschungsgemeinschaft, Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Wiley-VCH, Weinheim, Germany, p. 184.

DIN. 1972. Prüfung von Pigmenten; Teilchengrößenanalyse, Grundbegriffe (Testing of pigments; particle size analysis, basic terms). DIN 53206. Deutsches Institut für Normung, Berlin, Germany.

Dow Corning. 1972. One-year chronic dust inhalation toxicity study with J-DCA in albino rats and cynomolgus monkeys. Unpublished report. Industrial Bio-Test Laboratories, Northbrook, Illinois, USA. Dow Corning, Midland, Michigan, USA [Summary].

Table B.2: Hydrophobic SAS types (surface treated)

Type/ Product name	Producer	Treating agent
Pyrogenic		
Aerosil R809	Degussa	HMDS [a]
Aerosil R972	Degussa	DDS [b]
Aerosil R974	Degussa	DDS
Cab-O-Sil N70TS [c]	Cabot	PDMS [d]
Cab-O-Sil silane treated	Cabot	Unknown [e]
Cab-O-Sil ST20	Cabot	HMDS
Cab-O-Sil ST22 [f]	Cabot	HMDS
Cab-O-Sil TS500	Cabot	HMDS
Cab-O-Sil TS530	Cabot	HMDS
Cab-O-Sil TS610	Cabot	DDS
Cab-O-Sil TS720	Cabot	PDMS
D500	Degussa	Unknown
HDK SKS130	Wacker	HMDS
HDK SKS300	Wacker	HMDS
HDK SKS300 VI	Wacker	HMDS with vinyl function < 1%
HDK H15	Wacker	DDS
HDK H20	Wacker	DDS
HDK VP KHD15 [g]	Wacker	PDMS
HDK VP KHD50 [h]	Wacker	PDMS
J-DCA TX104	Dow Corning	HMDS

[a] Hexamethyldisilazane CAS 68909-20-6
[b] Dimethyldichlorosilane CAS 68611-44-9
[c] Also known as Cab-O-Sil TS720
[d] Polydimethylsiloxane CAS 67762-90-7
[e] Actual identity of this product remains unclear
[f] Previous name aminopropylsilane-treated pyrogenic SAS
[g] Current name HDK H2015EP
[h] Current name HDK H2050EP

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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 19, 2011

SUBJECT: Stability Testing Trimethylsiloxysilicate (Wacker-Belsil® TMS 803)

Habereder T. 2011. Memo to C Burger and M Strong regarding physical/chemical stability tests of Wacker-Belsil® TMS 803 (Trimethylsiloxysilicate)

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

WACKER

DR TASSILO HABEREDER
SPP-T7

Wacker Chemie AG
Johannes-Hess-Strasse 24
84489 Burghausen, Germany
Tel. +49 8677 83-8389
Fax +49 8677 3131
tassilo.habereder@wacker.com

MEMO

15.09.2011

To C. Burger M. Strong

cc

Wacker-Belsil® TMS 803 - Physical / Chemical Stability Tests

Dear Mike and Christa,

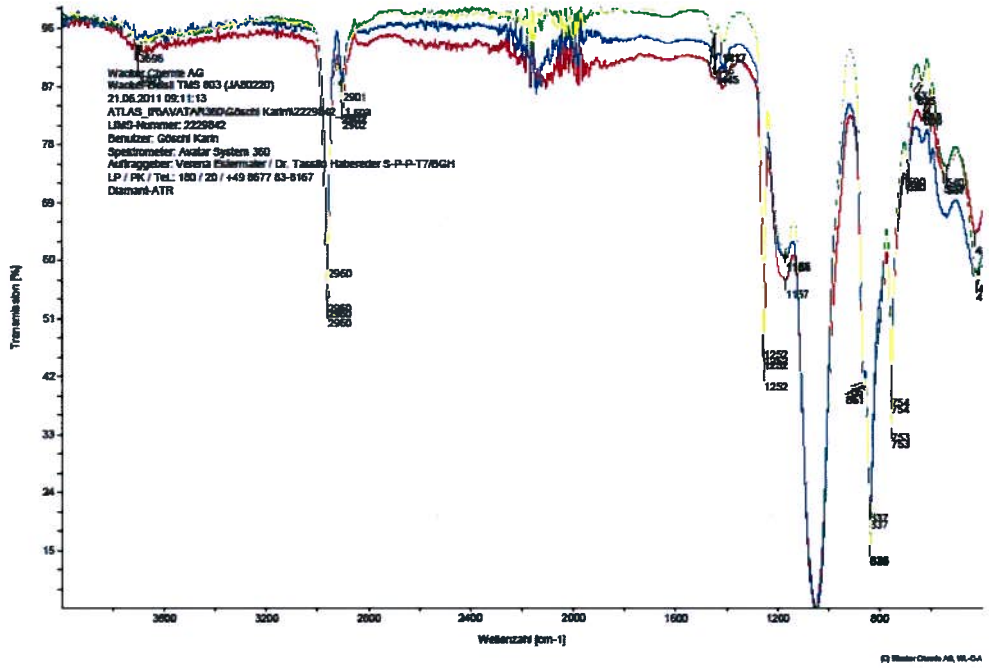
As agreed we have run temperature stability tests for our product Wacker Belsil® TMS 803. We applied two different tests:.

1) **Cycle testing**: The product was subject of the following thermal treatment. Five cycles of storage at -10°C for 24 hours and 45°C for 24 hours. Each cycle is completed after 2 days of temperature treatment at the mentioned temperature conditions. The product was characterized with IR and NMR measurements before and after the thermal treatment.

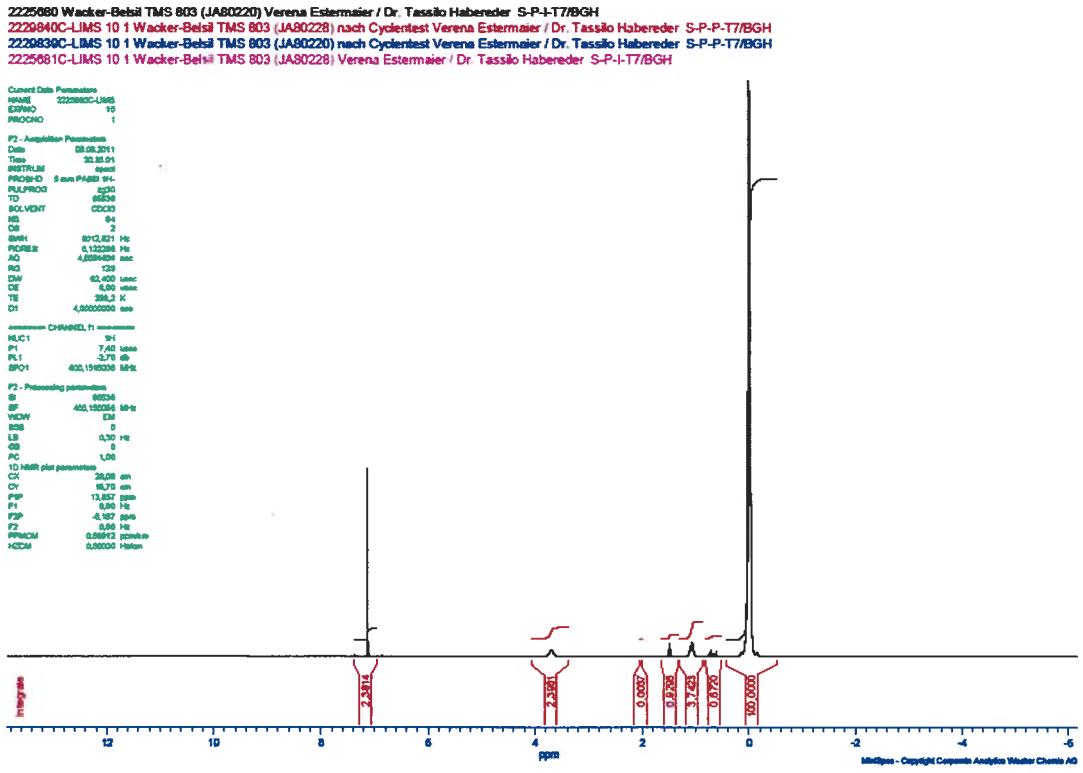
2) **Temperature variation test**: A sample of Wacker Belsil® TMS 803 was stored at 45°C for three months. The product was characterized with IR and NMR measurements before and after the thermal treatment.

Results of the Cycle testing:

The sample of Wacker Belsil® TMS 803 showed identical IR spectra before and after the thermal treatment in the cycle testing:



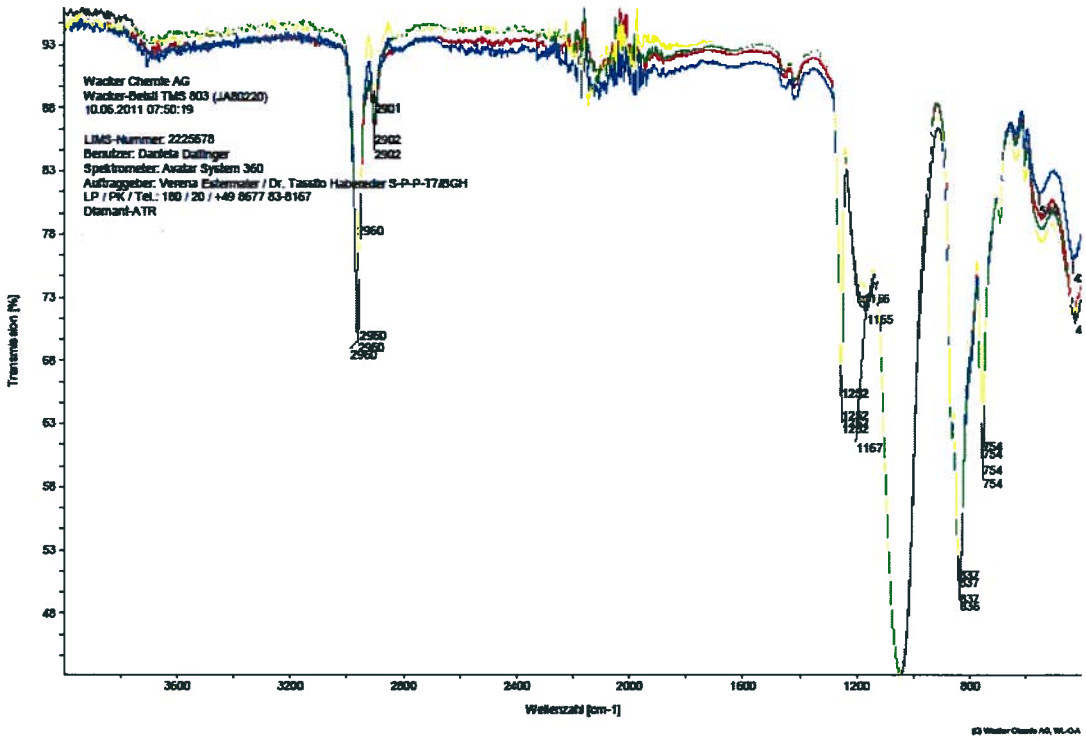
The sample of Wacker Belsil® TMS 803 showed also identical NMR spectra before and after the thermal treatment in the cycle testing:



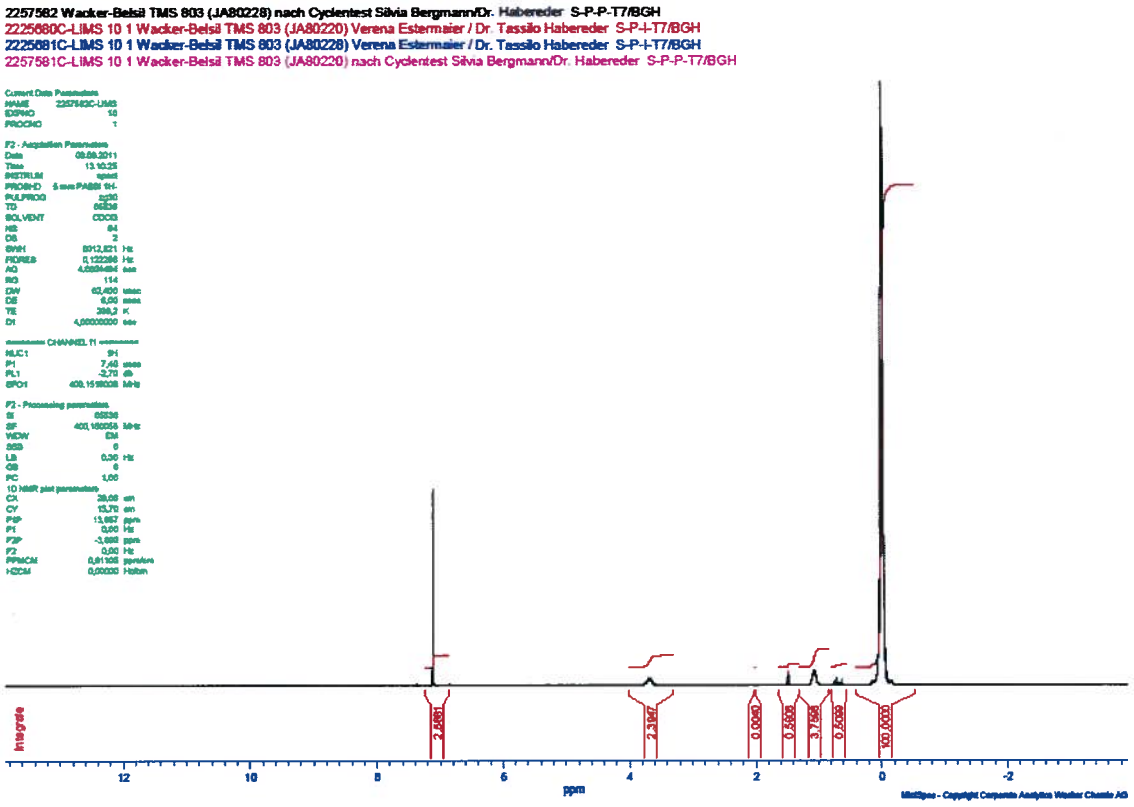
Therefore it can be concluded, that Wacker Belsil® TMS 803 is stable towards the conditions of the cycle testing.

Results of the Temperature variation test:

The sample of Wacker Belsil® TMS 803 showed identical IR spectra before and after the thermal treatment in the temperature variation test:



The sample of Wacker Belsil® TMS 803 showed identical NMR spectra before and after the thermal treatment in the temperature variation test:



Conclusion:

Wacker Belsil® TMS 803 bearing the INCI name TRIMETHYLSILOXYSILICATE, is silicone resin, which is thermally stable under the conditions of the tests: "Cycle testing" and "Temperature variation test". The obtained test results do fully match with the experiments which we have made using the material for several years as an additive in the cosmetic industry.

Best regards,

Dr. Tassilo Habereder