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Final Report on the Safety Assessment of Formaldehyde

ABSTRACT

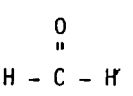
The report selectively reviews the extensive literature available on the toxicity of Formaldehyde. It is concluded that Formaldehyde in cosmetic products is safe to the great majority of consumers. Because of the skin sensitivity of some individuals to this agent, the formulation and manufacture of a cosmetic product should be such as to ensure use at the minimal effective concentration of Formaldehyde, not to exceed 0.2% measured as free Formaldehyde. It cannot be concluded that Formaldehyde is safe in cosmetic products intended to be aerosolized.

INTRODUCTION

The following report reflects the position of the CIR Expert Panel on the safety of formaldehyde in cosmetics. The report is a synopsis of the chemistry, use, biology and toxicology of formaldehyde. In developing this document, members of the Expert Panel reviewed selected references pertaining to formaldehyde safety, as well as a number of unpublished research reports[1,2] and published literature surveys.[3-12]

CHEMISTRY

Formaldehyde is a colorless, flammable, readily polymerizable gas having a pungent, suffocating odor. It has the following structural formula.[9,10,13,14]



Formaldehyde is generally supplied commercially as a 30%-56% (by weight) aqueous solution known as formalin. In aqueous solution, the dominant form of the formaldehyde is methylene glycol; in concentrated solution, it is one of many polymer molecules such as polyoxymethylene glycol. Formaldehyde is also available as its soild cyclic trimer, trioxane; and as its solid, linear, low-molecular-weight homopolymer, paraformaldehyde. Anhydrous gaseous formaldehyde is not available commercially.[8,10]

Formaldehyde is produced by the oxidation of methanol with air in the presence of a metal catalyst (silver or copper), or an iron-oxide molybdenum oxide catalyst.[10,15] When used in cosmetics, formaldehyde solution (formalin) typically has the following specifications: assay as HCHO: 37%–52%; assay as methanol: 1.5%–12%; acidity as formic acid: 0.04% maximum; iron: 2 ppm maximum; copper: 10 ppm maximum; ash: 0.01% maximum.[15] Methanol is present in formalin to inhibit polymerization.[9]

Formaldehyde is soluble in water, acetone, benzene, diethyl ether, chloroform, and ethanol.[10,13,16] In the absence of water, formaldehyde exists as a monomer and is stable. In the presence of small amounts of water, however, the gas may slowly trimerize to metaformaldehyde. When in aqueous solution, formaldehyde slowly polymerizes to form paraformaldehyde and other products including higher polymers of polyoxymethylene.[9] The uncatalyzed decomposition of formaldehyde is very slow below 300°C. The gas is relatively stable to polymerization at 80°–100°C, but slowly polymerizes at lower temperatures.[10] Decomposition products resulting from the photooxidation of formaldehyde include carbon monoxide, hydrogen, hydrogen peroxide, formic acid, and some other metastable products.[8] A proprietary stabilization process permits prolonged storage of formaldehyde.[15]

Formalin is a powerful reducing agent, especially in the presence of alkali. It is soluble in water, acetone and alcohol. In air, formalin slowly oxidizes to formic acid. Formation of various polymers may occur in formalin as evidenced by development of a cloudy solution; the rate of polymer formation is dependent on methanol content and storage temperature. On exposure of formalin to "very low" temperatures, a precipitate of trioxymethylene is formed.[8,10,13,16]

Paraformaldehyde is a colorless or white granular solid soluble in hot water or strong alkali solution, but insoluble in alcohol or ether. Its formula is $HO(CH_2O)_nH$, where n equals 8–100. The higher polymers of paraformaldehyde are insoluble in water. Paraformaldehyde is prepared by the evaporation of formalin. Commercial grades of paraformaldehyde usually contain not less than 95% formaldehyde by weight. At room temperature, paraformaldehyde gradually vaporizes to yield monomeric formaldehyde.[8,13,17]

Formaldehyde contains a highly reactive carbonyl group, and it undergoes chemical reactions typical of aldehydes. Among some of the reactions of formaldehyde are: hydration in the presence of water to yield $CH_2(OH)_2$; reaction with the active hydrogen of ammonia, amines or amides; reaction with other compounds having active hydrogens, such as thiols, nitroalkanes, hydrogen cyanide, and phenol; and condensation with HCL (and possibly other inorganic chlorides) in the presence of water to form the human carcinogen, bis(chloromethyl)ether.[6,18]* Formaldehyde is reported to undergo self-condensation, particularly under alkaline conditions. It may also condense with numerous compounds to produce methylol (CH_2OH) or methylene ($=CH_2$) derivatives.[10]

Reaction of formaldehyde with the active hydrogen of ammonia, amines or amides is of particular concern because of the ubiquity of nitrogen compounds

*Kinetic data of the hydrolysis of bis(chloromethyl)ether demonstrate that this carcinogen undergoes very fast unimolecular decompositions; half-life is approximately 10–40 sec at ambient temperature in aqueous media. Thus, bis(chloromethyl)ether cannot exist in aqueous solution for any extended period of time.[19]

(DNA, RNA, proteins, amino acids, etc.) in all biological systems. The reaction with purines and other amines yields an intermediate methylol product which is labile; the reaction product with a second amine moiety is stable.[6] Reaction of formaldehyde with the free amino group in protein probably accounts for the characteristic irritant effects of formaldehyde on mucous membranes.[9]

A diverse group of organic compounds, including alcohols, amines, amides, proteins, phenols, and hydrocarbons, form resins with formaldehyde. For example, urea and phenol can react with formaldehyde to form thermoplastic or thermosetting resins. These latter materials are widely used in the production of plywood, particleboard, foam insulation, and a variety of molded or extruded plastic items.[8,20] Formaldehyde may also react with acetaldehyde in the presence of a strong base to form pentaerythritol, a compound used in the production of various pharmaceuticals, plasticizers, insecticides, varnishes, resins, and esters.[15]

Various cosmetic ingredients such as albumin, casein, gelatin, agar, and starch may combine directly with formalin to form insoluble compounds. Formalin may also react with such cosmetic materials as perfume, coloring agents, ammonia, alkalies, iron preparations, and hydrogen peroxide.[13,21,22] Because of the highly reactive nature of formaldehyde, the possibility of its interaction with numerous other cosmetic ingredients should not be discounted.

It has been reported that aqueous solutions of formaldehyde generally contain less than 0.1% of the formaldehyde monomer. Polymeric forms of the monomer are the principle molecular species.[1,4] In the cosmetic product, it is not certain whether these same species predominate or if other condensation products or adducts are the predominant forms. It is reasonable to assume, however, that the free formaldehyde monomer concentration is a very small percentage of the amount of formaldehyde added to a cosmetic formulation, and that it exists in some equilibrium with the reacted monomer of polymeric forms.[1]

COSMETIC USE

Formaldehyde is typically used in cosmetics as a 37%–52% by weight aqueous solution.[15] The principal function of this cosmetic ingredient is that of an antimicrobial agent.[15,23] Both the concentration and antimicrobial effectiveness of formaldehyde in cosmetic products may decline over time.[21,22] Minimum inhibitory concentrations of formaldehyde against common cosmetic contaminants are presented in Table 1.

TABLE 1. Minimum Inhibitory Concentrations of Formaldehyde in ppm.[a]

Agar pH[b]	*Pseudomonas and other gram-negatives*	*Yeasts*	*Molds*	*Cocci*	*Bacillus sp.*
4	20–200	90–600	90	—	—
5.5	100–550	350–400	100–450	250	250
7	70–400	200–750	200–400	250	250

[a] Data from Ref. 24.
[b] Gradient plate method.

Data submitted to the Food and Drug Administration (FDA) in 1981 by cosmetic firms participating in the voluntary registration program indicated that this preservative (formaldehyde, paraformaldehyde and/or formalin) was used in a total of 805 formulations at concentrations of >5%–10% (2 products), >1%–5% (8 products), >0.1%–1.0% (429 products), and ≤0.1 percent (366 products) (Table 2).[25] Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations.[28] Since formaldehyde is primarily supplied for cosmetic use in a 37%–52% aqueous solution, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration might be one-third to one-half of that reported to the FDA (frequently, a reported concentration of "formaldehyde" is actually the concentration of formalin). The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

TABLE 2. Product Formulation Data for Cosmetics Containing Formaldehyde.[a]

Product category	*Total no. of products in product category*	*Total no. of products containing formaldehyde*	*No. of products containing formaldehyde at each percent concentration range*[b]			
			>5–10	*>1–5*	*>0.1–1*	*≤0.1*
Baby shampoos	35	7	—	—	4	3
Baby lotions, oils, powders, and creams	56	1	—	—	1	—
Bath oils, tablets, and salts	237	10	—	—	2	8
Bubble baths	475	109	—	—	25	84
Other bath preparations	132	24	—	1	5	18
Mascara	397	1	—	—	—	1
Other eye makeup preparations	230	3	—	—	1	2
Sachets	119	2	—	—	1	1
Hair conditioners	478	95	—	1	66	28
Permanent waves	474	11	—	—	6	5
Hair rinses (noncoloring)	158	32	—	—	18	14
Hair shampoos (noncoloring)	909	316	—	2	181	133
Tonics, dressings, and other hair grooming aids	290	21	1	1	13	6
Wave sets	180	37	1	—	20	16
Other hair preparations (noncoloring)	177	13	—	1	4	8
Hair dyes and colors (all types requiring caution statement and patch test)	811	5	—	—	—	5
Hair shampoos (coloring)	16	3	—	—	2	1
Face powders	555	1	—	—	1	—
Makeup foundations	740	2	—	—	1	1
Makeup bases	831	3	—	—	2	1
Cuticle softeners	32	1	—	—	—	1
Nail creams and lotions	25	1	—	—	—	1

TABLE 2. (Continued.)

Product category	Total no. of products in product category	Total no. of products containing formaldehyde	No. of products containing formaldehyde at each percent concentration range[b]			
			>5–10	>1–5	>0.1–1	≤0.1
Mouthwashes and breath fresheners (liquids and sprays)	53	2	—	—	1	1
Bath soaps and detergents	148	5	—	—	1	4
Deodorants (underarm)	239	7	—	—	7	—
Feminine hygiene deodorants	21	1	—	1	—	—
Other personal cleanliness products	227	1	—	—	—	1
Aftershave lotions	282	1	—	—	1	—
Shaving cream (aerosol, brushless, and lather)	114	2	—	—	—	2
Other shaving preparation products	29	1	—	1	—	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	13	—	—	9	4
Face, body, and hand skin care preparations (excluding shaving preparations)	832	47	—	—	37	10
Foot powders and sprays	17	1	—	—	1	—
Moisturizing skin care preparations	747	11	—	—	8	3
Night skin care preparations	219	5	—	—	3	2
Paste masks (mud packs)	171	3	—	—	2	1
Skin fresheners	260	1	—	—	1	—
Other skin care preparations	349	4	—	—	4	—
Suntan gels, creams, and liquids	164	2	—	—	1	1
1981 TOTALS		805	2	8	429	366

[a] Data from Ref. 25.

[b] Preset concentration ranges are used by firms in reporting data to FDA in order to conform to federal filing regulations outlined in 21 CFR 720.4.[28]

Cosmetic products containing formaldehyde, formalin and/or paraformaldehyde are applied to or have the potential to come in contact with hair (shampoos and hair preparations, etc.); skin (deodorants, bath products, skin preparations and lotions, etc.); eyes (mascara and eye makeup preparations, etc.); mouth mucosa (mouthwashes and breath fresheners); vaginal mucosa (feminine hygiene deodorants); and nails (cuticle softeners and nail creams and lotions). Aerosol products (shaving creams, for example) also present the potential that formaldehyde may be inhaled.

The FDA permits use of formaldehyde as an ingredient in nail hardeners provided that the product: (1) contains no more than 5% formaldehyde, (2) provides the user with nail shields which restrict application to the nail tip, (3) furnishes adequate directions for safe use, and (4) warns consumers about the consequences of misuse and potential for causing allergic reactions in sensitized users. The FDA has taken action against nail hardeners not meeting these safety requirements.[26]

The European Economic Community[27] has adopted a Directive which im-

poses concentration limits for formaldehyde and paraformaldehyde in cosmetics. These substances are permitted at maximum concentrations of 0.2% (expressed as free formaldehyde) in all cosmetic formulations except nail hardeners, oral hygiene products, and aerosol dispensers. Nail hardeners and oral hygiene products may contain maximum formaldehyde concentrations of 5% and 0.1%, respectively, whereas formaldehyde and paraformaldehyde are prohibited for use in aerosol dispensers (except for foams). Cosmetic product labels are required to list formaldehyde and paraformaldehyde as ingredients when the concentration of either exceeds 0.05%.

U.S. Federal regulations require that formaldehyde and other cosmetic ingredients be listed on the package of each cosmetic product in descending order of predominance. The labeling of ingredients is to "appear with such prominence and conspicuousness as to render it likely to be read and understood by ordinary individuals under normal conditions of purchase."[29]

NONCOSMETIC USE

Formalin is used as a preservative in many human and veterinary drugs and biologicals. Viral vaccines contain formalin at a level of 0.05% as an inactivating agent.[30] The numerous applications of formalin also include use in tissue preservation, embalming and vaccine production, pesticides, brake lining and pharmaceutical manufacturing, printing, insulation, plastic molding, and as a lubricant and ingredient in paint pigment.[31] The OTC Panel on Dentifrices and Dental Care Products has concluded that there are insufficient data to assess the effectiveness of formalin as a tooth desensitizer.[32,33]

Nearly three-fourths of the nine billion pounds of formaldehyde now produced annually in the United States is used in various resinous products. Formaldehyde is an essential component in urea–formaldehyde foam insulation, and wrinkle-resistant and shrink-proof textiles. It is also widely used as a binder and adhesive in the manufacture of paper, plywood and particleboard.[8] Federal regulations permit the use of formaldehyde as an indirect food additive in a number of materials having contact with food including adhesive coatings and components, acrylate ester copolymer coatings, resinous polymeric coatings, xylene–formaldehyde resins condensed with 4,4'-isopropylidene-diphenol-epichlorohydrin expoxy resins; zinc–silicon dioxide matrix coatings, paper and paperboard, defoaming agents used in coatings, defoaming agents used in the manufacture of paper and paperboard, cellophane (as urea formaldehyde), closures with sealing gaskets for food containers (as paraformaldehyde), phenolic resins in molded articles, textiles and textile fibers, and animal glue.[34-47] Formaldehyde is also allowed as a direct food additive in defoaming agents[48] and as an additive to animal feed.[49]

New installations of urea–formaldehyde foam insulation in residences and schools have been banned by the Consumer Product Safety Commission. The Commission's ban, effective August 10, 1982, is based on findings that suggest urea–formaldehyde foam insulation presents an unreasonable risk of injury from irritation, sensitization, and cancer because of the release of formaldehyde gas from the product after it is installed.[50,51]

BIOLOGY

Several recent documents provide detailed literature reviews of the published biological data on formaldehyde.[4,5,7-10,12] Unpublished information on the toxicity of cosmetic products containing formaldehyde noted in this document is available from the Cosmetic Ingredient Review.[1,2]

Normal Metabolism of One-Carbon Units

A dietary source of one-carbon units is essential (for example, from the methyl groups of methionine or choline). The vitamin folic acid functions as a metabolic carrier of the one-carbon units obtained from dietary and metabolic sources. The one-carbon derivatives of tetrahydrofolate provide methyl groups for such vital processes as the synthesis of DNA and for the control of protein synthesis. Tetrahydrofolate serves as a carrier of one-carbon units at three levels of oxidation corresponding to methanol, formaldehyde and formic acid. Under normal conditions, the content of free formaldehyde is very low in animal tissues. Sources include formaldehyde in equilibrium with N-5,N-10-methylene tetrahydrofolate and that which may be formed by the direct degradation of methionine, as well as by various demethylation reactions.[52] There is a formaldehyde-forming enzyme present in mammalian tissues (pig brain and rat kidney) that functions in the formation of certain alkaloids from, for example, dihydroxyphenylalanine.[53] Formaldehyde may also be formed in tissue by action of mixed function oxidases on the N-methyl groups of various xenobiotics.[54] Free formaldehyde in concentrations that exceed the dissociation constant of methylene tetrahydrofolate is quickly incorporated into the one-carbon pool.[52] Certainly, minor quantities of formaldehyde are encountered normally and are rapidly metabolized.[55]

Absorption, Metabolism, and Excretion of Exogenous Formaldehyde

Formaldehyde can enter the body through skin and ocular contact, inhalation, and ingestion. Once absorbed into the blood stream, formaldehyde disappears rapidly because of condensation reactions with DNA, protein, amino acids and other amines, as well as by oxidation to CO_2.[55] The half-life of formaldehyde in monkey blood has been estimated to be 1.5 min;[56] similar half-lives have been observed in the blood of rats, guinea pigs, rabbits, and cats.[57] The liver and erythrocytes appear to be primary sites of rapid oxidation of formaldehyde to formic acid and CO_2.[55] Rapid oxidation of formaldehyde to formate has also been shown to occur in many other tissues, including human brain; sheep liver; rat brain, kidney and muscle; rabbit brain; and bovine brain and adrenals.[58,59] The conversion of formaldehyde to formate has been observed following intravenous infusion, subcutaneous injection, gastric intubation and inhalation.[6] The plasma half-life of formate in dogs following i.v. infusion or oral administration of 0.2 *M* formaldehyde has been estimated to be 80–90 min.[58]

Oxidation of formaldehyde may be initiated by formation of S-formyl glutathione, which is then oxidized by nicotinamide–adenine dinucleotide, and finally cleaved by a thiol esterase releasing formic acid and glutathione.[59,60] Studies with rats, monkeys, and rat liver perfusates have demonstrated that the

primary pathway to CO_2 from formaldehyde and formate occurs via the tetrahydrofolate pathway.[61-64] Whereas the conversion of formaldehyde to CO_2 occurs in a similar manner in the different species studied, the relative importance of each reaction varies among species and tissues.[6] Thus, the rat is able to convert formate to CO_2 at more than twice the rate of monkeys (or humans) and, as a result, has lower blood formate levels and does not excrete formate in the urine.[65] With regard to tissue differences, mouse (C_3Hf/A) and hamster (Syrian Golden) lung tissue does not convert formate to CO_2 as efficiently as liver tissue.[66]

Absorption of formaldehyde through the upper respiratory tract of dogs was shown in one study to exceed 95% of the inhaled dose.[67] Humans exposed to formaldehyde gas (0.78 mg/m^3) for 3 h had a rapid rise in blood and urine formate concentrations.[68] Following subcutaneous injection of ^{14}C-formaldehyde into rats, approximately 81% of the radioactivity appeared as CO_2; a small amount of the radioactivity was found in choline.[69] In rats given formaldehyde by intraperitoneal injection, 82% of the radiolabel was recovered as CO_2, whereas 13%–14% was recovered as urinary methionine, serine and a cysteine adduct; it was postulated that CO_2 was derived from serine by deamination to pyruvate and oxidation in the Krebs cycle.[65] Incorporation of ^{14}C-formaldehyde into the nucleic acid protein fraction of WI 38 human diploid fibroblasts was also demonstrated; most of the radiolabel was found in RNA with lesser amounts in DNA and protein.[70]

Effect on Macromolecules of Biological Importance

The adverse effects of formaldehyde seen in many in vivo and in vitro systems may be related to its high reactivity with amines, and its formation of methylol adducts with nucleic acids, histones, proteins, and amino acids.[8] The irritant effects of formaldehyde on mucous membranes is likely the result of its reaction with the free amino group in proteins.[9] The interaction of formaldehyde with proteins and nucleic acids, particularly RNA, results in tissue fixation and denaturation; the denaturation observed with DNA is irreversible. If permanent cross-links are formed between DNA reactives sites and formaldehyde, these links could interfere with the replication of DNA and may result in mutations.[8]

Grafstrom et al.[71] recently suggested that formaldehyde could exert its mutagenic and carcinogenic efforts by both damaging DNA and inhibiting DNA repair. In their studies with cultured bronchial epithelial and fibroblastic cells from humans, formaldehyde induced DNA protein cross-links and DNA single-strand breaks at HCHO concentrations of 100 μM and 500 μM, respectively. Formaldehyde also inhibited the unscheduled DNA synthesis that occurs after exposure of cells to ultraviolet irradiation or to benzo[a]pyrene diolexpoxide, as well as inhibited the resealing of DNA single-strand breaks produced by ionizing radiation. It was suggested that the high reactivity of formaldehyde probably causes methylolation of chromatin or other proteins, including enzymes critical to DNA repair processes.

Animal Toxicology

LD_{50} values for formaldehyde in various species are given in Table 3.

Cosmetic products containing formaldehyde concentrations of 0.074% (2

TABLE 3. Acute LD_{50} Values for Formaldehyde in Various Species.

Species	*Route*	*LD_{50} (mg/kg)*	*Ref.*
rat	oral	800	72
	s.c.	420	73
	i.v.	87	74
mouse	s.c.	300	73
rabbit	dermal	270	75
guinea pig	oral	260	72

formulations) and 0.0925% (1 formulation) were shown to be nontoxic by ingestion.[1,2] Hair depigmentation was observed in black mice at the sites of subcutaneous injection of 100 μg of formaldehyde (as formalin).[76] Local necrosis was noted in rabbits following intrapulmonary administration of aqueous solutions of formaldehyde.[77,78] There was one report that mice treated with formaldehyde on the skin developed severe hepatic damage.[79]

Formalin produced severe skin irritation following application to rabbit skin using an occlusive dressing technique; however, no significant irritant effects were noted following exposure to a 1% aqueous solution of formaldehyde.[9] Cosmetic formulations containing 0.074% and 0.0925% formaldehyde were minimal to slight irritants to the skin of rabbits.[1,2] In studies with guinea pigs, 5%, 10%, and 20% aqueous solutions of formaldehyde, and 0.01% and 0.02% saline solutions of formaldehyde, were mildly to moderately irritating to the skin.[80]

Ocular irritation has been noted in animals exposed to formaldehyde vapor at concentrations of 15 ppm or more. Marked eye irritant effects, but no corneal injury were noted in both guinea pigs and rabbits exposed to 40–70 ppm formaldehyde for 10 days.[9] Cosmetic products containing 0.074% (2 formulations) and 0.0925% (1 formulation) formaldehyde were at most minimally irritating to the rabbit eye.[1,2] Severe ocular irritation was observed in rabbits given 15% formaldehyde in aqueous solution.[81]

Results of guinea pig sensitization studies varied according to formaldehyde concentration and test methodology. Formalin (37% formaldehyde in aqueous solution) elicited skin sensitization when tested by the Draize, Buehler, and Magnusson–Kligman maximization procedures.[82] In two separate studies in which the Buehler technique was employed, 2% formaldehyde in aqueous solution elicited sensitization,[9] whereas 5% formaldehyde in aqueous solution elicited no allergic reaction.[1,2] Skin sensitization was observed in guinea pigs following repeated intradermal dosing (optimization test); in this study, a 0.04% aqueous formaldehyde solution was used for induction.[9] In four separate guinea pig sensitization studies, the Magnusson–Kligman maximization test was used to evaluate formaldehyde in aqueous solution at various concentrations. Formaldehyde was sensitizing in two of these studies following induction and challenge applications of 2% and 0.8%, respectively. Formaldehyde was nonsensitizing to guinea pigs in a third study where the induction and challenge concentrations were 0.703% and 0.222%, respectively; as well as in a fourth study where the induction, booster, and challenge concentrations were 1.85%, 3.7%, and 0.925% (or 0.463%), respectively.[1,2]

Formaldehyde was administered for 90 days either in the drinking water of rats on a w/v basis at 50, 100, or 150 mg/kg/day; or, in the diet of dogs at doses of 50, 75, or 100 mg/kg/day. There were no significant changes observed in the organs examined microscopically, or in hematological and biochemical tests (hematocrit, hemoglobin, total and differential leukocyte counts, blood sugar, blood urea nitrogen, alkaline phosphatase, serum glutamic oxaloacetic transaminase). A decrease in weight gain was noted in the high dose group of each species.[83,84]

A 13-week study was conducted with rats to determine the dermal toxicity of a moisturizer containing 0.074% formaldehyde. The daily dose of formaldehyde was 2.3 mg/kg. There were no cumulative, systemic toxic effects. Urinalysis, clinical chemistry, hematologic values, appearance, behavior, survival, body and organ weights were normal, and no gross or microscopic lesions were found. Mild hyperkeratosis at the site of application was the only change noted which could be related to treatment.[1,2] Similar parameters were examined in another 13-week dermal toxicity study involving two cosmetic formulations. With each product, formaldehyde was applied daily to the rat skin at a dose of 1.78 mg/kg. At week seven, rats treated with one of the two products had a decrease in brain-to-body weight ratio, an altered neutrophile/lymphocyte ratio, increased uterine weight, and hyperkeratosis; other parameters were normal. No cumulative systemic toxicity was observed with either product.[1,2]

Acute, subacute, and chronic studies have been conducted in rats, mice, rabbits, guinea pigs, hamsters, cats, dogs, and monkeys to determine the effects of inhalation exposure to formaldehyde. These studies are reviewed extensively by Fielder.[9] Acute and subacute exposure to low (< 1 ppm) or moderate (10–50 ppm) concentrations of formaldehyde vapor is known to cause increased airway resistance, decreased sensitivity of the nasopalatine nerve, irritation of eyes and of the respiratory system, and changes in the hypothalamus. Exposure to high doses (> 100 ppm) of formaldehyde vapor can cause salivation, acute dyspnea, vomiting, cramps and death of the test animals.[10] Rats, guinea pigs, rabbits, monkeys and dogs exposed continuously to 3.7 ppm formaldehyde for 90 days exhibited interstitial inflammation of the lungs.[85]

Several recent inhalation studies have been reviewed by IARC.[10] Exposure of rats to 2.0, 5.6, or 14.3 ppm formaldehyde vapor 6 h/day, five days/week for up to 24 months resulted in a variety of nasal cavity lesions including dysplasia and squamous metaplasia of respiratory epithelium, and purulent or sero-purulent rhinitis. Similar lesions were observed in mice exposed for the same length of time to 5.6 or 14.3 ppm formaldehyde; whereas, no effects were observed after exposure to 2 ppm.[86] Acute cellular degeneration, necrosis and inflammation were present in the nasal mucosa of rats exposed to 15 ppm formaldehyde vapor 6 h/day for 1–9 days.[87] Hyperplasia of respiratory epithelial cells has been observed in rats and mice exposed to 15 ppm formaldehyde 6 h/day for three days.[87] In yet another study, monkeys, rats, and hamsters were exposed to 0.0, 0.02, 1.0, or 3.0 ppm formaldehyde vapor for 22 h/day, seven days/week for 26 weeks. Squamous metaplasia of the nasal turbinate epithelium was evident in 6/6 monkeys at 3 ppm and in 1/6 at 1 ppm; squamous metaplasia and basal cell hyperplasia of the respiratory epithelium were significantly increased in rats exposed to 3 ppm. No exposure-related effects were observed in the hamsters.[88]

Rats and mice are obligatory nose breathers; therefore, nasal defense

mechanisms may be more important in these animals. Thus, with respect to target organs for formaldehyde, it may be inappropriate to extrapolate results of rat and mouse formaldehyde-inhalation experiments directly to humans.[8]

Special Studies

Embryotoxicity/Teratogenicity

The International Agency for Research on Cancer has concluded there are insufficient data to evaluate adequately the embryotoxicity/teratogenicity of formaldehyde.[10]

Formaldehyde was given to pregnant CD-1 mice as an aqueous solution (containing about 0.2% formaldehyde) at oral doses of 74, 148, and 185 mg/kg on Days 6–15 of gestation. The 185 mg/kg dose was lethal by Day 18 to most of the females (23/34), but no deaths were noted at the 74 mg/kg dose; one rat of the mid-dose group died. The number of resorption sites was increased and mean litter size was decreased slightly in the high dose group; these parameters were normal in the other two dose groups. No effects on fetus size, and no skeletal or visceral abnormalities (gross or microscopic) were observed.[89]

No teratogenic effects were observed in the offspring of pregnant beagles given formaldehyde at dietary concentrations of 125 or 375 ppm on Days 4–56 of gestation. No compound-related effects were noted in the female parents. Litter size, number of stillborn pups, and pup survival were not different from controls. A few of the pups were observed for up to nine months, during which time no abnormalities were noted in appearance or behavior.[90]

In an inhalation study, female rats were exposed continuously at reported concentrations of 0.012 mg/m^3 (0.01 ppm) or 1 mg/m^3 (0.8 ppm) from 10 days prior to mating and throughout the gestation period. No gross malformations occurred in fetuses at either dose level, and the only evidence of toxicity in females was a slight increase in the length of the gestation period. Average weight of offspring from both treatment groups was increased at birth. At necropsy of the neonates, the weights of thymus, kidney, and adrenal were increased and liver and lung weights were decreased.[91]

No alteration of reproductive function was seen in male rats given formaldehyde for six months at 0.1 ppm in drinking water, or 0.4 ppm in air.[92]

Mutagenicity

The mutagenicity of formaldehyde has been reviewed.[8-10,93,94] There is evidence that formaldehyde does not react with native double stranded DNA, but that it does react with single stranded DNA, or "open" DNA in which the hydrogen bond is disrupted.[9] Grafstrom et al.[71] recently suggested that formaldehyde could exert its mutagenic and carcinogenic effects both by damaging DNA and inhibiting DNA repair.

The mutagenic activity of formaldehyde has been demonstrated in studies with bacteria *(Escherichia coli, Pseudomonas fluorescens, Staphylococcus aureus);* RNA containing virus; yeast *(Saccharomyces cerevisiae);* fungi *(Neurospora crassa, Aspergillus nidulans);* grasshopper *(Tristria pulvinata)* and fruitflies (larval and adult *Drosophila*). The mutagenic effect of formaldehyde in *Drosophila melanogaster* is dependent on the route of administration. Both positive and negative mutagenic results have been obtained with *Salmonella*

typhimurium. Formaldehyde did not induce mutations in the silkworm *(Bombyx mori)*.[8-10]

The mutagenic activity in various mammalian systems has also been studied. An increase in the mutation frequency was observed when formaldehyde was tested in the L5178Y mouse lymphoma assay,[95,96] but not in the Chinese hamster ovary cell assay.[97] No mutagenic effect was noted in a dominant-lethal study in which Swiss mice were given intraperitoneal injections of formaldehyde; however, it should be noted that several known mutagens were inactive in this test as well.[98] Early fetal deaths and preimplantation losses in Q strain mice were reported after males were given intraperitoneal injections of formaldehyde, but no chromosomal aberrations were observed in preparations of meiotic spermatocytes from the treated animals.[99] Treatment of C3H/10T1/2 Cl eight mouse embryo fibroblasts with formaldehyde did not result in significant rates of transformation; however, when formaldehyde exposure was followed by continuous treatment with the tumor promoter 12-0-tetradecanoyl phorbol-13-acetate, transformed foci were produced.[100] Formaldehyde has also been shown to induce sister chromatid exchanges in cultured Chinese hamster ovary cells and human lymphocytes;[101] unscheduled DNA synthesis in Hela cells;[102] preferential killing of xeroderma pigmentosum cells;[103] DNA-protein crosslinks in both mouse L1210 cells[104,105] and Chinese hamster V79 cells;[87] and transformation in mouse BALB/c 3T3 cells.[10]

The relevance of these studies is difficult to assess for any systemic, mutagenic, or carcinogenic effects in mammals since it is known that formaldehyde is rapidly metabolized in the bloodstream, and hence, may be detoxified before it can produce critical damage to cellular DNA.[9]

Carcinogenicity

In a recent study at the Chemical Industry Institution of Toxicology (CIIT), groups of B6C3F mice and Fischer 344 rats were exposed to 0, 2.0, 5.6, or 14.3 ppm (0, 2.0, 6.9, 17.6 mg/m^3) formaldehyde (>97.5% pure) vapor by whole body exposure for 6 h/day, 5 days/week for up to 24 months. Animals were killed at 6, 12, 18, 24, 27, and 30 months. Histopathological examinations were made of the tissues lining the nasal cavity as well as tissues from each major organ system. In mice of the high-dose group, the incidence of nasal mucosal squamous cell carcinoma was not statistically significant. However, the incidences of a variety of nonneoplastic lesions of the nasal mucosa were significantly increased at formaldehyde concentrations of 5.6 and 14.3 ppm.[86] In rats exposed to 14.3 ppm, a significant increase in the incidence of nasal mucosal squamous cell carcinoma was noted; no other neoplasm was significantly increased. The incidences of a variety of nonneoplastic lesions of the nasal mucosa were also significantly increased in rats at formaldehyde concentrations as low as 2 ppm; these increased in extent and severity with increasing concentrations.[86,106]

With regard to the CIIT study, signs of chronic irritation to the nasal passages were noted prior to the development of the tumors. It has been suggested that the marked increase in cell turnover associated with chronic irritation is necessary for the expression of any mutagenic effects of formaldehyde on the cells of the nasal turbinate.[9]

In a second inhalation study, 100 Sprague–Dawley rats were exposed from

nine weeks of age to 14.2 ppm (17.23 mg/m^3) formaldehyde vapor for 6 h/day. After a total of 382 exposures over a period of 588 days, 10 histologically confirmed, grossly visible nasal squamous-cell carcinomas were observed. No nasal tumors were seen in 1,920 control rats over a period of 14 years.[107]

Ninety-nine Sprague–Dawley rats were exposed from eight weeks of age to a mixture of 14.7 ppm (17.9 mg/m^3) formaldehyde vapor and 10.6 ppm (17.3 mg/m^3) hydrogen chloride gas 6 h/day, 5 days/week for life. The average concentration of bis(chloromethyl)ether (BCME) formed was 1 ppb (5.13 ng/m^3). Of the exposed animals, 28 developed nasal tumors (25 had squamous cell carcinomas and three had papillomas). No nasal tumors were seen in controls.[107]

Various reports indicate that BCME, a recognized human carcinogen, should not be formed in substantial amounts if concentrations of both hydrogen chloride and formaldehyde gas are less than 100 ppm at ambient temperature and humidity.[8] However, Frankel et al.[108] found that BCME was formed in glass vessels at less than 0.5 ppb when formaldehyde and hydrogen chloride are each present at 20 ppm.

C3H mice were exposed to formaldehyde vapor at concentrations of 0, 0.05, 0.1, or 0.20 mg/l (0, 50, 100, or 200 mg/m^3) for 1 h/day, three times per week for 35 weeks. There were no pulmonary tumors in any dose group. The nasal epithelium was not examined either grossly or microscopically. Basal cell hyperplasia and squamous and atypical metaplasia were seen in the trachea and bronchi of treated mice. In the same experiment, an additional group of mice were exposed to 100 mg/m^3 formaldehyde vapor for 35 weeks and then to a coal-tar aerosol for 35 weeks; the formaldehyde did not modify the pulmonary carcinogenesis of coal tar.[109]

Ten rats were injected subcutaneously once weekly for 15 months with 1 ml of 0.4%–0.5% formaldehyde in aqueous solution. Sarcomas were observed in four rats: two in the skin at the injection site, one in the liver, and one in the peritoneal cavity. No control animals were used.[110]

Hamsters were given 10 weekly subcutaneous injections of 0.5 mg N-nitrosodiethylamine concurrently with weekly 5-hour exposures to 30 ppm (36.7 mg/m^3) formaldehyde for life. The number of tumors per tumor-bearing animal of the "concurrently exposed group" was increased over the group receiving N-nitrosodiethylamine alone.[111]

Hamsters were exposed in an inhalation study to 10 ppm formaldehyde five times/week (5 h/day) for life. No tumors were observed in sections of respiratory tract tissues from either unexposed or treated animals. In a separate experiment, hamsters were exposed once per week to 30 ppm formaldehyde (5 h/day) for life. No tumors were observed in the respiratory tract of the formaldehyde-only control group; however, hamsters exposed to formaldehyde at two days prior to each of 10 weekly diethynitrosamine injections had a higher incidence of tracheal tumors/tumor-bearing animal at necropsy than those receiving diethynitrosamine alone.[112]

Six rabbits were fitted by a muzzle-like holder to tanks containing a 3% formaldehyde solution for 90 min, five times per week for 10 months. Animals were sacrificed after 11 months of exposure. Leucoplakia was grossly visible in 2/6 rabbits; in these lesions, dyskeratosis and intraepithelial carcinoma of the exposed mucosa were confirmed microscopically.[113]

The International Agency for Research on Cancer concluded "there is sufficient evidence that formaldehyde gas is carcinogenic to rats." They noted that

concentrations of formaldehyde that cause nasal tumors also cause acute degeneration, necrosis, inflammatory changes and increased cell replication (hyperplasia) of the nasal mucosa of rats and mice following inhalation exposure.[10]

The evidence of formaldehyde-induced neoplasia in rats had led the National Institute of Occupational Safety and Health to recommend that this material be handled as a potential human carcinogen.[114]

Clinical Assessment of Safety

Table 4 summarizes data on human responses to formaldehyde at various airborne concentrations. The severity of specific health effects appears to be dose-related.[8] Among some of the reported effects are neurophysiologic changes (as demonstrated by alterations in optical chronaxy, EEG, etc.); eye, skin, nose, throat, and bronchial irritation; and pulmonary lesions (pneumonia, bronchial inflammation, pulmonary edema). Death may result from exposure to formaldehyde vapor at concentrations of 100 ppm and greater.[8,9] The effects of formaldehyde arising from occupational exposure have been reviewed in some detail by Fielder.[9] The American Conference of Governmental Industrial Hygienists recommends a limit of 2 ppm (approximately 2.5 mg/m^3) for occupational exposure.[14]

Formaldehyde is intensely irritating to the eyes. Ocular irritation to atmospheric formaldehyde generally occurs at concentrations of 0.05–0.5 ppm; lacrimation occurs at concentrations of 4–20 ppm. Aqueous solutions of formaldehyde accidently splashed into the eye have caused such injuries as eyelid and conjunctival edema, corneal opacity, and loss of vision.[8,9] Numerous studies demonstrating the eye irritating ability of formaldehyde have been reviewed by the National Research Council.[8]

Upper airway (nose and throat) irritation to formaldehyde vapor frequently occurs at 1–11 ppm (irritation has been recorded at concentrations as low as 0.1 ppm). Formaldehyde can cause alterations in the nasal defense mechanisms, which may include a decrease in mucociliary clearance and loss of olfactory sensitivity. Lower airway irritation frequently is reported at 5–30 ppm. Chest radiographs of persons exposed to these concentrations are usually normal, ex-

TABLE 4. Reported Human Health Effects of Formaldehyde at Various Airborne Concentrations.[a]

Health effects reported	*Approx. formaldehyde conc. (ppm)*
None	0–0.05
Neurophysiologic effects	0.05–1.50
Odor threshold	0.05–1.0
Eye irritation	0.01–2.0[b]
Upper airway irritation	0.10–25
Lower airway and pulmonary effects	5–30
Pulmonary edema, inflammation, pneumonia	50–100
Death	100+

[a] Data from Ref. 8.

[b] The low concentration (0.01 ppm) was observed in the presence of other pollutants that may have been acting synergistically.

cept for occasional reports of accentuated bronchovascular marks; however, pulmonary function tests may be abnormal. Pulmonary edema, and pneumonitis and death can result from very high airborne formaldehyde concentrations (50–100 ppm).[8]

Formaldehyde inhalation has been shown to cause bronchial asthma and asthma-like symptoms in humans. Although asthmatic attacks are in some cases specifically attributable to formaldehyde sensitization or allergy, the gas seems to act more commonly as a direct airway irritant in persons who have bronchial asthmatic attacks from other causes. The exact mechanism for asthma induction by formaldehyde is not known.[8]

Formaldehyde has been reported to cause contact urticaria, and it is a known skin irritant and sensitizer. Allergic contact dermatitis in persons both occupationally and nonoccupationally exposed to formaldehyde is well recognized.[9] The North American Contact Dermatitis Group reported a 5% incidence of skin sensitization (124 reactors) among 2,374 patients exposed to 2% formaldehyde in aqueous solution.[115] Most sensitized persons can tolerate topical axillary products containing formaldehyde at up to 30 ppm;[116] with increasing concentrations, a higher frequency of responders is seen.[117] The National Research Council reported that aqueous formaldehyde solutions elicit skin responses under occlusive conditions in some sensitized individuals at concentrations as low as 0.01%. It was also noted that underarm products containing up to 0.003% formaldehyde are tolerated by most sensitized individuals.[8] In unpublished data reported by the Cosmetic, Toiletry and Fragrance Association, cosmetic products containing 0.000185%–0.0925% formaldehyde were practically nonirritating and nonsensitizing in a total of 1,527 subjects in 18 separate tests (Table 5). Bruynzeel et al.[118] have noted that allergens which are marginal skin irritants such as formaldehyde, often give weak positive reactions which may be lost at retesting.

Jordan et al.[116] have evaluated threshold skin sensitization responses to formaldehyde in formaldehyde-sensitive individuals. In one double-blind experiment, closed patches containing 0, 30, or 100 ppm formaldehyde in a vehicle of water and 12 percent methanol were applied to the upper backs of nine formaldehyde-sensitive subjects. Patches were applied on Friday and reapplied the following Monday (72 h) and Wednesday (120 h). The last reading was conducted on Friday (168 h). Four nonallergic control subjects underwent identical testing. Results for the formaldehyde-sensitive subjects are presented in Table 6. By the 168 hr. reading, a total of six of nine subjects reacted to 100 ppm, five of nine reacted to 60 ppm, and four of nine to 30 ppm. None of the four nonallergic control subjects reacted to 0, 30, 60, or 100 ppm formaldehyde in the methanol-in-water vehicle. In a second experiment, 13 formaldehyde-sensitive subjects pump-sprayed 28.86 ppm formaldehyde in a methanol-in-water vehicle into one axilla twice per day for two weeks. The vehicle served as a control in the opposite axilla. Two of 13 subjects exhibited minimal dermatitis, whereas another three individuals had subjective complaints of itching or burning skin. No responses to the vehicle were seen. Findings from these two studies indicate that formaldehyde concentrations below 30 ppm can be tolerated by most sensitive subjects when repeatedly applied to normal skin. According to Jordan et al.[116] any response on normal, semioccluded skin should be a "very mild, self-limited problem, provided no additional therapeutic insults are added."

The dose needed to elicit a skin sensitization response depends on such fac-

TABLE 5. Human Skin Irritation and Sensitization to Cosmetic Products Containing Formaldehyde.

Type of test	*Material tested*	*Actual Formaldehyde conc. tested (%)*	*Method*	*No. of subjects*	*Results*	*Ref.*
Skin irritation	Skin moisturizer containing 0.25% formalin.[a]	0.0925	24 h occlusive patch	20	Nineteen subjects showed no skin reactions and one had a "barely perceptible" erythemic response. The PII[b] was 0.03.	119
Skin irritation	Noncoloring hair rinse containing 0.2% formalin.[a]	0.074	24 h occlusive patch	20	Nineteen subjects showed no skin reaction and one had a "barely perceptible" erythemic response. The PII[b] was 0.03.	120
Skin irritation	Facial cleanser containing 0.2% formalin.[a]	0.074	21 daily applications under an occlusive patch	8	Three of eight subjects showed cumulative skin irritation. The three reactors had a total cumulative score of 19/504 to the facial cleanser, whereas the test group as a whole had a total cumulative score of 299.5/504 to the positive control.[c] The average cumulative scores to the facial cleanser and positive control were 2.38 and 37.44, respectively.	121
Skin irritation	Skin cleanser containing 0.2% formalin.[a]	0.074	24 h occlusive patch	20	No skin irritation observed. The PII[b] was 0.	122
Skin irritation	Skin Cleanser containing 0.2% formalin.[a]	0.074	24 h occlusive patch	19	No skin irritation observed. The PII[b] was 0.	122
Skin irritation	Skin Cleanser containing 0.2% formalin.[a]	0.074	24 h occlusive patch	19	Eighteen subjects showed no skin reaction and one had a mild erythemic response. The PII[b] was 0.05.	122

Skin irritation/ sensitization	Facial Cleanser containing 0.2% formalin.[a]	0.074	RIPT[d]	204	Two subjects showed one or more skin reactions (1+ and 2+) to the induction patches. Two others showed skin reactions (1+) on challenge as well as to the induction patches (1+ and 2+). One of the latter two subjects agreed to a follow-up rechallenge with the product "as is" under occlusion, diluted 1:4 under occlusion, and "as is" under semi-occlusive conditions. The material was applied three times daily for five consecutive days. At 48 h, a 1+ reaction was noted in the subject under "as is" occluded conditions. No reaction was osbserved at 96 h. No reactions were observed at 48 or 96 h under the "diluted occlusive" or the "as is semi-occlusive" regimens. The investigators determined that this was evidence of an irritant reaction, and was not sensitization. The other subject who had reacted at challenge declined to participate in the rechallenge. It was noted that this subject had reacted to several other materials being evaluated, and she was categorized as an "angry back" type subject. The facial cleanser was considered to possess a minimal potential for inducing irritant or allergic contact dermatitis under foreseeable conditions of product use.	123

TABLE 5. (Continued.)

Type of test	*Material tested*	*Actual Formaldehyde conc. tested (%)*	*Method*	*No. of subjects*	*Results*	*Ref.*
Skin irritation/ sensitization	Facial Moisturizer containing 0.1% formalin.[a]	0.037	RIPT[d]	200	None of the subjects had any skin changes as a result of the first induction application. During subsequent induction applications, six subjects showed skin reactions determined to be "artifacts" on the procedure in that the changes were minimal, of less than 24 h duration, noncumulative in producing scores of 2+ or greater, and not consistently repetitive. One subject showed irritant responses considered to be evidence of skin fatigue. On challenge none of the subjects showed any response.	124
Skin irritation/ sensitization	Hair care product containing 0.2% formalin.[a] The product was tested in aqueous soln. at 25%.	0.0185	RIPT[d]	101	Four subjects exhibited one or more skin reactions (minimal to moderate erythema) during the induction phase. No subjects reacted on challenge.	125
Skin sensitization	Medicated cleanser containing 0.2% formalin.[a]	0.074	NR[e]	83	No sensitization observed.	126
Skin sensitization	Liquid cleanser containing 0.1% formalin.[a] The product was diluted so that it was tested in aqueous soln. at 0.5%.	0.000185	NR[e]	83	No sensitization observed.	126
Skin sensitization	Moisturizer containing 0.2% formalin.[a]	0.074	NR[e]	118	No sensitization observed.	126

Skin sensitization	Cleansing cream containing 0.2% formalin.[a]	0.074	NR[e]	118	No sensitization observed.	126
Skin sensitization	Hand cream containing 0.1% formalin.[a]	0.037	NR[e]	113	No sensitization observed.	126
Skin sensitization	Moisturizer containing 0.2% formalin.[a]	0.074	NR[e]	92	No sensitization observed.	126
Skin sensitization	Hair treatment product containing 0.2% formalin.[a] The product was diluted so that it was tested in aqueous soln. at 25%.	0.0185	NR[e]	98	No sensitization observed.	126
Skin sensitization	Hair conditioning rinse containing 0.2% formalin.[a] The product was diluted so that it was tested in aqueous soln. at 25%.	0.0185	NR[e]	98	No sensitization observed.	126
Skin sensitization	Daytime moisturizer containing 0.1% formalin.[a]	0.037	NR[e]	113	No sensitization observed.	126
			Total	1527		

[a] Formalin: 37% (w/w) aqueous formaldehyde solution.

[b] PII = Primary Irritation Index: a value depicting the average skin response of the test panel as a whole. It is calculated by adding the irritation scores and dividing by the total no. of test subjects. The PII is based on a scale of 0 (no skin reaction) to 4 (severe skin erythema and/or edema).

[c] For each subject, scores were graded daily on a scale of 0 to 4; however, testing ceased when a score of 3 was reached. A score of 3 was then recorded thereafter for each of the remaining days that the subject was not tested. Thus, for 8 subjects over 21 days of testing, the maximum possible score was 504 ($8 \times 21 \times 3 = 504$).

[d] RIPT = Repeat Insult Patch Test. Each induction application was made every other day for 3 weeks for a total of 9–10 induction exposures. The challenge application followed 10–14 days after the induction phase. Scores were based on a scale of 0 (no skin reaction) to 4+ (marked erythema and edema).

[e] NR = Not reported.

TABLE 6. Number of Formaldehyde-Sensitive Subjects Having Allergic Responses.[a,b]

Formaldehyde (ppm)	*72 h*	*120 h*	*168 h*	*Total*
0	0	0	0	0/9
30	1	2	1	4/9
60	2	2	1	5/9
100	3	2	1	6/9

[a] Data from Ref. 116.

[b] Patch tests applied on Friday with reading and reapplication on Monday (72 h) and Wednesday (120 h). Final reading Friday (168 h).

tors as skin penetration (skin penetration of formaldehyde varies from one person to another and from one skin site to another); occlusion; temperature; contact time (minimal with shampoos and other "rinse-off" cosmetics); and vehicle.[8] The Cosmetic, Toiletry and Fragrance Association has noted the following with respect to formaldehyde sensitization:[1]

> In terms of sensitization potential for Formaldehyde, it has been demonstrated and reported in published literature that formalin can induce sensitivity in both laboratory animals and humans. There does appear to be a threshold for the induction of sensitization as well as for the elicitation of a response in previously sensitized individuals. There are various factors that might be expected to ameliorate the sensitization potential of Formaldehyde in a cosmetic formulation. These factors play a role in determining the Formaldehyde monomer and complexes available in the formulation and their ability to penetrate the skin barrier, and include the other ingredients present in the formulation and whether they potentiate or diminish the sensitization potential of the Formaldehyde present. Another factor of primary importance to the induction of sensitization is the exposure or normal use characteristics of the product. All of these factors are considered, as well as the efficacy of the Formaldehyde as a preservative with the particular formulation when preparing a cosmetic product.

Skin sensitization to cosmetic products may result from a number of formaldehyde-releasing agents used in formulations. It has been reported that formaldehyde-releasing preservatives, such as Quaternium-15, show a greater reaction frequency than formaldehyde itself.[8] Quaternium-15 at the usual preservative concentration of 0.1% releases about 100 ppm of free formaldehyde. Repeated topical application of creams and lotions utilizing Quaternium-15 can pose a problem for formaldehyde-sensitive individuals.[116]

Ingestion of formaldehyde has been reported to cause allergic reactions, corrosive effects on the gastrointestinal and respiratory tracts, and systemic damage. Following ingestion, there may be loss of consciousness, vascular collapse, pneumonia, hemorrhagic nephritis, fatty degeneration of the liver, "involvement of the brain," and spontaneous abortion. Death may occur after the swallowing of as little as 30 ml of formalin. Paresthesia, soft-tissue necrosis and sequestration of bone have occurred when formaldehyde preparations were used for devitalization of dental pulps.[8]

Central nervous system responses to formaldehyde have been evaluated in a

variety of ways including determination of optical chronaxy, electroencephalography, and by the sensitivity of dark-adapted eyes to light. Responses are observed in some individuals at 0.05 ppm formaldehyde and are maximized at approximately 1.5 ppm.[8]

Hemolytic anemia occurred in patients undergoing chronic hemodialysis following contamination of the dialysis water with formaldehyde. Subsequent in vitro experiments to determine the mechanism of formaldehyde action revealed that the substance converts NAD to NADH in the erythrocyte. The alteration of the redox state leads to inhibition of glycolysis at the level of glyceraldehyde 3-phosphate dehydrogenase and rapid decline in cellular ATP content. A formaldehyde concentration as low as 0.1 m*M* caused decreased ATP content in erythrocytes, whereas the maximal inhibiting effect on red blood cell metabolism occurred after exposure to 1.0 m*M* formaldehyde.[127]

Numerous studies have been conducted to determine the incidence of cancer and mortality in industries where formaldehyde is used. However, these studies are of limited value since workers in such industries were exposed to many other chemicals in addition to formaldehyde.[10]

Medical personnel, particularly pathologists and certain laboratory technicians, have an increased likelihood of exposure to formaldehyde.[10] According to data recorded in the Danish Cancer Registry during 1943–1976, only three cases of cancer of the nasal cavities, sinuses, or nasopharynx were observed in Danish doctors. None of these three doctors had ever worked in a pathology department or as anatomists.[128] In a mortality study of pathologists and medical laboratory technicians in the U.K., male pathologists had a significant increase in lymphoid and hematopoietic neoplasms, but similar findings were not observed in the laboratory technicians.[129] In a study of 34,400 British doctors, no significant increase in respiratory cancers was found among nonsmokers.[13] The mortality rates within 11 occupation groups (including scientific research, pathology and biochemistry) among 20,540 male doctors indicated reduced numbers of oral, esophageal and pulmonary cancer.[131]

The result of three recent mortality studies of workers using formaldehyde or manufacturing formaldehyde and other chemicals were inconclusive. In a study of embalmers who used embalming fluid containing formaldehyde and a variety of other chemicals, a proportional excess of deaths from skin cancer was observed.[132] Mortality as a result of skin cancer increased with both duration of employment in embalming and intensity of exposure (as judged by whether a person was involved in both embalming and funeral directing or just in embalming). The group involved only in embalming had increased proportional mortality from cancers of the kidney and brain; there was no proportionate excess of deaths from respiratory cancer and no deaths from cancer of the nose or nasal sinuses. In a second study of white male employees of a chemical factory where formaldehyde and a variety of other chemicals were manufactured, overall mortality was significantly less than expected.[133] In addition, the number of deaths observed from all cancers equalled that expected. However, excess numbers of deaths over those expected occurred from Hodgkin's disease as well as prostatic and brain cancers. The number of deaths from respiratory cancer equalled that expected, and there were fewer digestive system cancers than expected. There were no deaths from cancers of the nose or nasal sinuses. Analysis of causes of deaths that occurred more than 20 years after first employment in the factory indicated a significant excess of deaths from prostatic cancer. In a third mortality

study of white and nonwhite male employees from a chemical plant where formaldehyde was both produced and used as a raw material in the production of other chemicals, a proportional excess of deaths from digestive-tract cancer was reported for white workers.[134] These latter individuals were each exposed to formaldehyde for a total of less than five years. Cancers of the nose or nasal cavities were not observed among the workers. It should be noted that the number of deaths observed after a suitable latent period in all three of the aforementioned studies was small and would be insufficient to show increased risk of an uncommon cancer.[10]

The International Agency for Research on Cancer has concluded that epidemiological studies to date provide inadequate evidence to assess the carcinogenicity of formaldehyde in man. Several epidemiological studies to determine the relationship between formaldehyde and cancer are currently in progress.[10]

DISCUSSION

Formaldehyde is a useful compound manufactured on a huge scale and employed as such or in various forms in numerous industries and in a wide variety of products. It seems unlikely that one can escape exposure to this compound in one form or another whether it be at work, at home, in the clothes we wear, or in air contamination from combustion engines or tobacco smoke. In low amounts, it is generated and present in the body as a normal metabolite, and as such or when taken into the body it is rapidly metabolized by several pathways to yield carbon dioxide. It is a very reactive chemical.

Because of this reactivity, it is both useful and hazardous. It is useful as an ingredient in cosmetic formulations principally for the prevention of microbial contamination, but for other reasons as well. It is an irritant at low concentration, especially to the eyes and the respiratory tract in all people. It induces hypersensitivity, but not as often as might be expected, considering the frequency and extent of exposure. Under experimental conditions it is teratogenic, mutagenic and it can induce neoplasms.

Perhaps the single most important attribute common to these toxic effects of formaldehyde is that they are all concentration/time dependent. Formaldehyde can be employed usefully at concentrations that do not induce lacrimation, or irritation to the nose or throat. Still higher concentration/duration exposure than that which produces irritation induces degenerative changes in the tissues exposed to it. For that matter, there is no evidence that formaldehyde can induce neoplasia at concentration/time relationships that do not damage normal structure and function of tissues, even under laboratory conditions. It may or may not be relevant that no creditable epidemiological studies in humans support a carcinogenic potential for formaldehyde.

It is expected that there will be future studies on the carcinogenic potential of formaldehyde. It is possible that some of these studies will suggest or demonstrate that formaldehyde is an activator of known carcinogens, that it combines with other normal body constituents to cause cancer, or that perhaps it acts as a cocarcinogen. Such work will have to be judged on its own merits and as a part of total knowledge of the safety or hazard of formaldehyde.

ANALYSIS OF SUBMITTED COMMENTS

The CIR Expert Panel publicly reviewed submitted comments relating to the use of formaldehyde at a concentration of 4.5% in nail hardeners.* In its deliberations, the Panel concurred that the submitted evidence was inadequate to assure that formaldehyde could be safely used above 0.2% in cosmetic products. Further information on the Panel's discussion regarding nail hardeners may be found in the Minutes of the CIR Expert Panel meeting held on July 25–26, 1983.

CONCLUSION

Formaldehyde in cosmetic products is safe to the great majority of consumers. The Panel believes that because of skin sensitivity of some individuals to this agent, the formulation and manufacture of a cosmetic product should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0.2% measured as free formaldehyde. It cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized.

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