# Final Amended Report

## Formaldehyde and Methylene Glycol

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# ABSTRACT

Methylene glycol is continuously converted to formaldehyde, and vice versa, even at equilibrium, which can be easily shifted by heating, drying, and other conditions to increase the amount of formaldehyde. This rapid, reversible formaldehyde/methylene glycol equilibrium is distinguished from the slow, irreversible release of formaldehyde resulting from so-called formaldehyde releaser preservatives, which are not addressed in this safety assessment (formaldehyde releasers may continue to be safely used in cosmetics at the levels established in their individual CIR safety assessments).

Formaldehyde and methylene glycol may be used safely in cosmetics if established limits are not exceeded, and are safe for use in nail hardeners in the present practices of use and concentration, which include instructions to avoid skin contact. In the present practices of use and concentration (on the order of 10% formaldehyde/methylene glycol, blow drying and heating, inadequate ventilation, resulting in many reports of adverse effects), hair smoothing products containing formaldehyde and methylene glycol are unsafe.


# INTRODUCTION

In 1984, CIR published its original safety assessment of formaldehyde,[1] concluding that this ingredient is safe for use in cosmetics applied to the skin if free formaldehyde was minimized, but in no case > 0.2%. This conclusion was based on data from numerous human skin irritation and sensitization tests (number of subjects ranging from 8 to 204) of cosmetic products (skin cleansers and moisturizers and a hair rinse) containing 0.2% formalin (37% w/w aqueous formaldehyde solution). Except for a few mild, equivocal, or inconsistent reactions, the results of these tests showed that such products have little potential to irritate or sensitize the skin. The Panel also said that it cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized.

The Panel re-reviewed the safety assessment of formaldehyde and confirmed the original conclusion in 2003.[2]

Since that re-review, methylene glycol has been listed as a cosmetic ingredient and CIR has become aware of increasing uses of formaldehyde/methylene glycol in hair smoothing products intended to be heated. In addition to the issues related to increasing uses and identification of methylene glycol as a cosmetic ingredient, the U.S. EPA National Center for Environmental Assessment (NCEA) released a draft toxicological review of formaldehyde for external review on 2 June 2010, including interagency comments on an earlier draft of the document.[3] The NCEA Risk Assessment provides a comprehensive summary of the toxicological literature, including both human and animal studies and all of the major exposure routes of concern (inhalation, ingestion, and skin contact). The U.S. National Research Council (NRC) has released their review of the draft assessment.[4] Much of the significant new toxicology data are related to genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

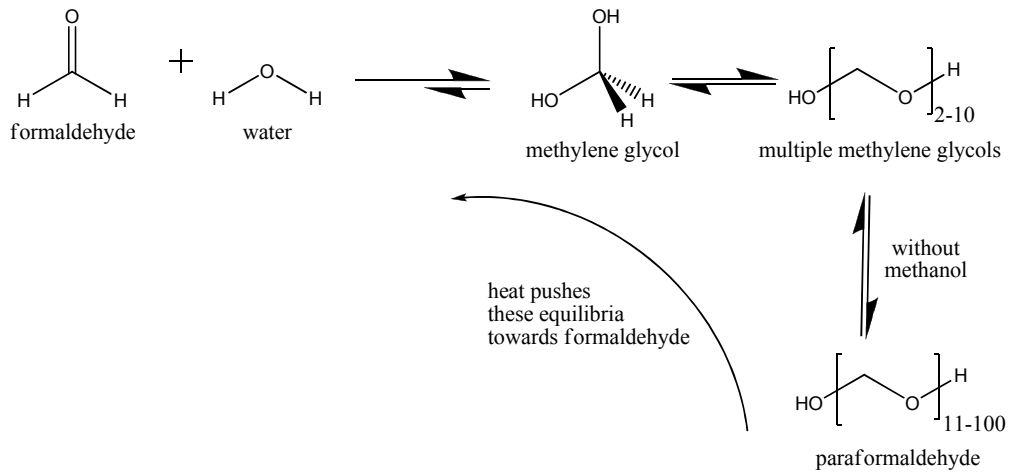
Data and analysis were provided by the Nail Manufacturer's Council (NMC) the Professional Keratin Smoothing Council (PKSC), the Personal Care Products Council, and the American Chemistry Council. Additional data from the U.S. Food and Drug Administration's (FDA's) adverse event reporting system and results of FDA laboratory product analyses are included.

# CHEMISTRY

### Formaldehyde – Formalin –Methylene Glycol

Formaldehyde, a gas, is not used in cosmetics in its pure, anhydrous form, but is instead most commonly produced as an aqueous solution called formalin.[5] Formalin is industrially produced from methanol. First, a mixture of vaporized methanol and steam is passed over a catalyst bed, where the methanol is oxidized to formaldehyde gas. Since this reaction is highly exothermic, the gas stream is cooled directly after passing over the catalyst to prevent thermal decomposition. Next, the formaldehyde reacts with water in an absorption column, because formaldehyde in its pure, gaseous form is highly unstable. Formaldehyde quickly reacts with water to produce methylene glycol and, without a polymerization inhibitor (eg, methanol), polymethylene glycols via a series of reversible reactions (Scheme 1). In the absence of methanol, these reactions proceed to form a mixture of long chain polymethylene glycols, which are referred to as paraformaldehyde.

**Scheme 1 – Equilibria in aqueous formaldehyde solutions such as formalin**




Methylene glycol, as a pure and separate substance, is not commercially available, but is instead produced as an aqueous solution called formalin, as denoted above for formaldehyde. Methylene glycol is a *geminal* (*gem*) diol, or a diol with both hydroxyl groups on the same carbon. *Gem* diols are typically unstable compounds. Indeed, methylene glycol exists only in aqueous solution, where it is stabilized by hydrogen bonding with water molecules. Thus, the high solubility of formaldehyde in water is due to the rapid hydration of formaldehyde to methylene glycol and the capacity of the aqueous solution to stabilize methylene glycol and small polymethylene glycols (ie, two to ten methylene glycol units long).[6] The rate of the hydration reaction is very fast (the half-life of formaldehyde in water is 70 milliseconds) and the equilibrium between methylene glycol and formaldehyde strongly favors methylene glycol at room temperature and neutral pH.[7] The equilibrium is dependent on temperature, solution density, pH, and the presence of other solutes. Increased temperature favors formation of formaldehyde. While the concentration of methylene glycol in formalin is much greater than formaldehyde, at room temperature, neutral pH stasis, this says nothing about the reversibility of this equilibrium shift or about the rate of dehydration when this stasis is disrupted (eg, formalin is exposed to air or a formulation containing formalin is heated). This reaction is reversible. The dehydration of methylene glycol to formaldehyde happens rapidly and can be catalyzed by lower pH.[8]

The formation of the higher polymethylene glycols is much slower than the rates of hydration and dehydration, and can be inhibited by methanol. Accordingly, a typical solution of formalin consists of water (~40-60%), methylene glycol (~40%), methanol (~1-10%), small methylene glycols (eg, dimers and trimers; ~1%), and a very small amount of formaldehyde (~0.02-0.1%). The multiple equilibria between these components favor methylene glycol at room temperature.[9] However, removal of water, increase in solution density, heating, reduction of pH, and/or the reaction of the small amount of free formaldehyde in the solution will drive the equilibrium back toward formaldehyde.[10] Moreover, a product formulated with either of the ingredients methylene glycol or formaldehyde actually contains an equilibrium mixture of the components: methylene glycol, polymethylene glycols and formaldehyde. While it can be pointed out that formaldehyde and methylene glycol are different and distinct molecules, the ever present equilibrium between the two makes this distinction of virtually no relevance to ingredient safety.[11] Due to the equilibria demonstrated above, any aqueous formulation that reportedly contains formalin, formaldehyde, or methylene glycol, actually contains both formaldehyde and methylene glycol. Accordingly, the ingredients formaldehyde and methylene glycol can be referred to as formaldehyde equivalents. Under any normal conditions of cosmetic use, including at room temperature and above, methylene glycol is not stable in the gas phase and very rapidly dehydrates to formaldehyde and water.[12] Accordingly, heating of a formulation containing formaldehyde or methylene glycol will primarily off-gas formaldehyde. For this reason, the hazards of formaldehyde equivalents in a heated solution are the same as the hazards of gaseous formaldehyde, since the solution so readily releases gaseous formaldehyde.

## Formaldehyde Equivalents

Formalin, as recited above, is an aqueous solution of formaldehyde, methylene glycol and polymethylene glycols, all in equilibria and often stabilized with methanol. Formalin, *per se*, is not listed as an ingredient in the International Cosmetic Ingredient Dictionary and Handbook (INCI Dictionary) but is often recited herein as the material tested (therefore representing formaldehyde/methylene glycol). Of special importance is an understanding of the meaning of percent formalin. "100% formalin" means an aqueous solution wherein formaldehyde has been added to water to the saturation point of these equilibria, which is typically 37% (by weight) formaldehyde equivalents in water. Accordingly, a 10% formalin solution contains approximately 3.7% formaldehyde equivalents. More specifically, an aqueous solution which is 3.7% of formaldehyde (by weight) relates directly to a solution which is 5.9% methylene glycol (because the molecular weight of formaldehyde is 30 g/mol and the molecular weight of methylene glycol is 48 g/mol).

All of the toxicity studies relied upon for determining the current 0.2% limitation in cosmetic products are based on the idea of "free formaldehyde," what we now are calling formaldehyde equivalents. However, it seems quite probable that this number actually meant 0.2% formalin. Accordingly, based on the average formalin solution being 37% formaldehyde equivalents, this represents a true limit of 0.074% formaldehyde equivalents.

Moreover, the ingredients in this review are not to be confused with "formaldehyde releasers," which are not analogous to formaldehyde or methylene glycol, but release small amounts of formaldehyde over considerable intervals (eg, Diazolidinyl Urea), acting as preservatives.

## Analytical Methods

Most commonly used analytical methods for qualitative and quantitative detection of formaldehyde are non-specific to non-hydrated formaldehyde, but can accurately describe formaldehyde equivalent presence and quantity. A typical method, for example the method used by the Oregon OSHA Laboratory, can detect formaldehyde equivalents present in a formulation, or released into the air, via a two stage process: 1) derivatization of a sample with a hydrazine (which reacts with formaldehyde or methylene glycol, in a formulation sample or in an air sample), and 2) detection of the resultant hydrazone (ie, the reaction product of the hydrazine and formaldehyde) with a diode array, after separation on a column (eg, high performance liquid chromatography (HPLC) separation followed by ultraviolet/visible light (UV/Vis) detection).[11] Accordingly, published values for "formaldehyde" levels should be taken to mean formaldehyde equivalents.

While other formaldehyde/methylene detection techniques are known, the methods used by OSHA are the most common methods and are what current regulations, globally, have been based on. These techniques would find that a typical formalin solution contains approximately 37% formaldehyde equivalents. Some may argue that using nuclear magnetic resonance (NMR) spectrometry techniques would demonstrate that this same formalin solution is only 0.037% formaldehyde.[13] This is a technically correct interpretation of the amount of non-hydrated formaldehyde molecules present in the static environment of an NMR sample tube. This scenario, however, exists only in the highly controlled experimental system where the conditions (room temperature, neutral pH, closed NMR tube) maintain an artificially constant level of non-hydrated formaldehyde. This does not represent the conditions under which formaldehyde or methylene glycol are used in hair smoothing products, and as such, drastically underestimates the exposure risk. In use, hair smoothing treatments containing formaldehyde or methylene glycol involve elevated temperatures (eg, 450 degrees F) and reduced pH formulations (eg, as low as pH = 4).[13] Further, the solutions are used in a system where the bottle is opened, the solution is poured, applied, and allowed to partially evaporate/off gas. Focusing on the equilibrium between formaldehyde and methylene glycol in a closed system that artificially favors a liquid state is not representative of the conditions of use of these ingredients in hair smoothing products.

An alternative technique has also been proposed for specifically addressing the vapor/gas present in the headspace above an aqueous formaldehyde/methylene glycol solution, which involves trimethylsilyl (TMS) derivatization of those moieties present, followed by detection of the resultant derivatives.[13] However, the chemical specificity for this method is not conclusively defined. The resultant derivatives detected could have arisen from a variety of constituents present in the headspace. Furthermore, no standards were recited which validate this method's ability to detect non-hydrated formaldehyde.

# COSMETIC USE

As given in the INCI Dictionary,[14] formaldehyde functions in cosmetic products as a cosmetic biocide, denaturant, and preservative. According to the 2010 13th Edition of the INCI Dictionary, methylene glycol is reported to function as an artificial nail hardener.[14]

In the FDA's Voluntary Cosmetic Registration Program (VCRP),[15] there are 77 uses of formaldehyde and formaldehyde solution (formalin) reported. Since these all are probably the same ingredient as added to cosmetics, they are combined in Table 1.[2,15,16] Industry surveys of formaldehyde use concentrations and an FDA reports yielded data shown in Table 1.[16-19] No uses of methylene glycol are currently reported to the VCRP, but the use concentration in nail hardeners containing methylene glycol reportedly ranges from 0.8% to 3.5% (corresponding to 0.5% to 2.2% calculated as formaldehyde).[16-19]

The Material Safety Data Sheet (MSDS) provided by Brazilian Blowout for their salon product, however, does include methylene glycol.[20] The list of ingredients provided by the manufacturer is shown in Table 2, with methylene glycol listed at <5.0%.

From a high of 805 reported uses of formaldehyde/formalin in 1984, VCRP data from 2001/2002, 2006/2007, and 2009/2010 show that uses have decreased to less than 100 uses, as shown in Figure 1. The VCRP, however, does not include reporting of ingredients used in cosmetics labeled "for professional use."

In Europe, formaldehyde is also permitted for use in cosmetics at concentrations ≤0.2% (the limit for oral hygiene products is ≤0.1%).[21] Products containing >0.05% formaldehyde must be labeled "contains formaldehyde." The maximum authorized concentration in finished nail hardeners is 5%, provided that the product is labeled "Protect cuticles with grease or oil. Contains formaldehyde" These limits are expressed as "free formaldehyde" or "calculated as formaldehyde." Formaldehyde is prohibited for use in aerosol dispensers. Canada, Australia, China and ASEAN nations have regulatory limits very similar to those of the European Union.[22-27]

### Use of Formaldehyde/Methylene Glycol in Nail Hardening Products

The FDA Guide to Inspections of Cosmetic Product Manufacturers[28] states that nail hardeners often contain formaldehyde as the active ingredient and that the Agency has not objected to its use as an ingredient of nail hardeners if the product 1) contained no more than 5% formaldehyde, 2) provided the user with nail shields that restrict application to the nail tip (and not the nail bed or fold), 3) furnished adequate directions for safe use, and 4) warned consumers about the consequences of misuse and potential for causing allergic reactions in sensitized users. Based on comments given at the June 27-28, 2011 CIR Expert Panel meeting, it appears that nail shields are no longer supplied with nail hardeners in the U.S. because consumers did not use the shields.

As noted above, in Europe, formaldehyde is permitted for use in nail hardeners at concentrations ≤5% "calculated as formaldehyde," and the product label must instruct the user to protect cuticles with grease or oil.[29] If the formaldehyde concentration in the product exceeds 0.05%, the label must also state "contains formaldehyde."

In the earlier CIR safety assessment of formaldehyde,[1] the CIR Expert Panel acknowledged reports of use of formaldehyde in nail hardeners at a concentration of 4.5%. It now appears that methylene glycol is considered to be the appropriate ingredient name to use to describe formaldehyde/methylene glycol in nail hardeners. [14] . Recent data provided by the Nail Manufacturers Council (NMC)[30] indicated that, to make a nail hardener nominally "1% formaldehyde"– which should be considered a typical marketplace level – a formulator would add 2.703% formalin (2.703% x 37% = 1%). Because of the well-recognized equilibrium relationship between formaldehyde and methylene glycol, the formaldehyde converts to methylene glycol. Therefore, a product with 2.703% formalin would contain 1.60% methylene glycol (2.703% x 59.2% = 1.60%). A recent survey of U.S. marketers conducted by the NMC indicated that formaldehyde/methylene glycol is not used in all brands of nail hardeners.[18] The survey results indicated that brands using methylene glycol/formaldehyde contain 0.7% to 1.85%, calculated as formaldehyde. Analyses of two finished nail hardener products (brand/origin not identified) indicated that they contained 1.9% and 2% formaldehyde equivalents, expressed as formaldehyde.[19] FDA recently reported finding 2.2% formaldehyde/methylene glycol in a nail hardening product that was cited often in a compilation of customer self-reports from Internet sites indicating adverse effects including skin irritation, burning sensation of nail beds and

exposed skin, and pain[17,31] and two cases of eyelid dermatitis reported by a member of the CIR Expert Panel. The cases reported by the Panel member patched tested negative for 1% formaldehyde equivalents (calculated as formaldehyde) in water; higher concentrations (eg, 2%) were not tested.

### Use of Formaldehyde/Methylene Glycol in Hair Smoothing Products

The use of formaldehyde/methylene glycol containing hair smoothing products largely appears to take place in salons, but use in a home is not precluded. Workplace surveys conducted by the Oregon Occupational Safety and Health Administration (OSHA) uncovered a wide variety of ventilation approaches, including simply having a building HVAC system, propping the business's doors open, or operating ceiling fans.[11]

Although the purpose and mechanism of action of formaldehyde/methylene glycol in hair relaxers/straighteners is not well documented, formaldehyde (as part of a formalin solution) is known to induce a fixative action on proteins (eg, keratin).[32] This is at least in accord with formaldehyde's function as a denaturant, in the classic sense of the term (ie, reacting with biological molecules, such as disrupting the tertiary structure of proteins, not just making liquids non-potable). Purportedly, formaldehyde/methylene glycol hair straightening formulations, such as Brazilian-style or keratin-based straightening products, maintain straightened hair by altering protein structures via amino acid crosslinking reactions, which form crosslinks between hair keratins and with added keratin from the formulation.[33]

One proposed reaction scheme involves: 1) hemiacetal formation between a keratin hydroxyl group and formaldehyde, 2) reaction of two such hemiacetals, in a dehydration step, to form a methylene ether crosslink, and 3) formaldehyde elimination to finalize the new methylene crosslink.[34] Stoichiometricaly, this proposed scheme purports that some of the formaldehyde that initially reacts with keratin is eventually released as formaldehyde during the hair straightening process. Formaldehyde can react with multiple protein residue side-chains, although the principal reactions are with the epsilon amino groups of lysine residues.[35] Besides proteins, formaldehyde is known to react with other biological molecules such as nucleic acids and polysaccharides.[36] The action of formaldehyde in intramolecular and intermolecular crosslinking of macromolecules can considerably alter the physical characteristics of the substrates.

The U.S. OSHA has issued a hazard alert concerning hair smoothing products that could release formaldehyde into the air.[37] The alert stated that OSHA investigations uncovered formaldehyde concentrations greater than OSHA's limits of exposure.[38] One investigation reported such levels of formaldehyde even though the product was labeled "formaldehyde-free." The hazard alert stated that formaldehyde gas presents a health hazard if workers are exposed, described the other chemical names to look for on the label that would signal reason for concern, and told businesses what to do to reduce exposure when using formaldehyde-releasing hair smoothing products.

Canada issued health advisories informing consumers of the risks associated with hair smoothing products containing excessive levels of formaldehyde, and has recalled several such products.[39-42] Hair smoothing products with formaldehyde at levels >0.2% are not permitted for sale in Canada.[41]

France's health authority warned consumers and hairdressers against using hair straightening treatments that contain high levels of formaldehyde and has removed a number of such products from the market.[43] Germany's Federal Institute for Risk Assessment (BfR) advised against the use of hair straightening products that contain formaldehyde in high concentrations.[44] The Irish Medicines Board, which is the competent authority in Ireland for cosmetics, took action to remove hair smoothing products from the market if they contain greater than 0.2%, the level established by the European Commission (EC).[45]

## TOXICOKINETICS

Formaldehyde is a highly water-soluble, reactive, rapidly metabolized chemical with a relatively short biological half-life. Inhaled formaldehyde is absorbed primarily in the respiratory epithelium lining the upper airways, where it undergoes extensive local metabolism and reactions with macromolecules. Based on the weight of the evidence, the NRC concluded that formaldehyde does not penetrate beyond the superficial layer of the nasopharyngeal epithelium, and is unlikely to appear in the blood as an intact molecule, except possibly at concentrations high enough to overwhelm the metabolic capacity of the epithelium.[4] The NRC concluded that formaldehyde is not

available systemically in any reactive form, and systemic effects are unlikely from the direct delivery of formaldehyde or methylene glycol to distal sites, except possibly in highly exposed people.

# TOXICOLOGY

## Previous CIR Safety Reports on Formaldehyde- Summary

In low amounts, formaldehyde 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. Not surprisingly, formaldehyde is an irritant at low concentrations, especially to the eyes and the respiratory tract. Formaldehyde exposure can result in a sensitization reaction. Under experimental conditions formaldehyde is teratogenic, mutagenic and can induce neoplasms.

Perhaps the single most important attribute common to these toxic effects of formaldehyde is that they are all concentration/time dependent. A higher concentration or duration of exposure than that which produces irritation, for example, induces degenerative changes in the tissues exposed to it. There was 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.

*From the Final Report on the Safety Assessment of Formaldehyde*[1]

New clinical studies reviewed in 2003 confirmed that formaldehyde can be a skin irritant and sensitizer, but at levels higher than the 0.2% free Formaldehyde upper limit established by the CIR Expert Panel.

The developmental toxicity, genotoxicity, and carcinogenicity of high doses of formaldehyde were also confirmed in the new studies (published between 1984 and 2003). These studies demonstrated that there is a threshold effect; that is, high doses are required before any effect is seen.

*From the Published Re-Review of Formaldehyde*[2]

## New Data on Safety of Formaldehyde

The U.S. EPA National Center for Environmental Assessment (NCEA) released a 4-volume draft toxicological review of formaldehyde for external review on 2 June 2010, including interagency comments on an earlier draft of the document.[3] U.S. EPA is conducting this assessment to support the development of new chronic inhalation toxicity values for formaldehyde. Ultimately, the final versions of these values will be incorporated into the U.S. EPA Integrated Risk Information System (IRIS).

The NRC recently released their review of U.S. EPA's draft assessment [4] and their findings are also summarized below, where appropriate. The NRC noted that the systemic delivery of formaldehyde may not be required for some of the systemic effects attributed to formaldehyde inhalation (eg, lymphohematopoietic cancers and reproductive toxicity). Instead, systemic effects could be secondary, indirect effects of the local effects of exposure, including local irritation and inflammation, and stress.

This document provides a summary of the toxicological literature, including both human and animal studies and all of the major exposure routes of concern (inhalation, ingestion, and skin contact). Much of the significant new toxicology data are related to genotoxicity, carcinogenicity, and reproductive and developmental toxicity. A comprehensive summary of the findings is presented in Tables 3 through 11.

## Reproductive and Developmental Toxicity

Several potential modes of action of formaldehyde for reproductive and developmental outcomes have been suggested by animal studies, including endocrine disruption, genotoxic effects on gametes, and oxidative stress or damage.[46,47] However, the evidence for causality is weak. In addition, it is not clear that inhaled formaldehyde or its metabolites can penetrate past the portal of entry or cross the placenta, blood-testis barrier, or blood-brain barrier.

The findings of studies on male reproduction generally used concentrations that result in significant weight loss and overt toxicity. There are no multigenerational tests for reproductive function.[3] These deficiencies, particularly for

male reproductive effects, represent important data gaps in the assessment of risks of reproductive and developmental toxicity associated with inhalation exposures to formaldehyde.[4]

The NRC noted that a small number of epidemiological studies[48-51] suggest an association between occupational exposure to formaldehyde and adverse reproductive outcomes in women.[4]

## Genotoxicity

Clear evidence of systemic mutagenicity does not emerge from animal inhalation bioassays, despite the reactivity and mutagenicity demonstrated in isolated mammalian cells.[52-54]

Similarly, the evidence that inhaled formaldehyde may be directly genotoxic to humans systemically is inconsistent and contradictory.[55-60]

## Carcinogenicity

### *Nasopharyngeal Cancers (NPC)*

The NRC agreed with EPA that there is sufficient evidence from the combined weight of epidemiologic findings, results of animal studies, and mechanistic data of a causal association between the inhalation of formaldehyde and cancers of the nose, nasal cavity, and nasopharnyx.[4] Formaldehyde is highly reactive, readily forms DNA and protein adducts and crosslinks, and is a direct-acting genotoxicant. Among the potential modes of action that have been considered for the development of NPCs through the inhalation of formaldehyde in animal studies include direct mutagenesis of cells at the site of first contact and cytotoxicity-induced cell proliferation (CICP), which correlates with tumor incidence.[61-68]

The subchronic or chronic inhalation of formaldehyde at high concentrations (eg, ≥6 ppm) clearly can cause NPCs in mice and rats. However, there is still debate in the scientific community about whether this effect should be considered to be a non-threshold effect or a threshold effect in cancer risk assessments.

The NRC concluded that these two primary modes of action contribute to formaldehyde-induced carcinogenicity in nasal tissues, including mutagenicity and CICP.[4] A mutagenic mode of action is generally the reason for adopting the default low-dose linear extrapolation methods in a quantitative cancer risk assessment. However, the NRC noted that formaldehyde is endogenous, that nasal tumors are rare in both rats and humans, and that no increases in tumor frequency are observed in animal studies at formaldehyde concentrations that do not also cause cytotoxicity. Further, the animal studies reveal a substantial nonlinearity in dose-response relationships among formaldehyde uptake, cytotoxicity, cell proliferation, and tumor formation.

Thus, the NRC recommended that the quantitative assessment of the risks of formaldehyde-induced NPCs incorporate the nonlinear phenomenon of CICP, as well as the mutagenicity of formaldehyde.[4]

### *Lymphohematopoietic (LHP) Cancers*

The three proposed modes of action by which formaldehyde exposure may cause leukemia include:[69]

- Transport of formaldehyde/methylene glycol from the portal of entry through the blood to the bone marrow, followed by direct toxic action to hematopoietic stem cells in the marrow
- Direct toxic action of formaldehyde/methylene glycol on circulating blood stem cells and progenitors at the portal of entry, followed by return of the damaged cells to bone marrow
- Direct toxic action of formaldehyde/methylene glycol on primitive pluripotent stem cells at the portal of entry, followed by migration of damaged cells to bone marrow

Similarly, direct toxic action of formaldehyde/methylene glycol on lymphocytes in mucosa-associated lymphoid tissues (MALT) at the portal of entry may cause lymphoid cancers.[3]

Remarkably little evidence from animal studies indicates that formaldehyde exposure can cause LHP cancer. Studies have consistently failed to find elevated levels of free formaldehyde or methylene glycol in the blood of exposed human and animal subjects, or DPCs in the bone marrow of exposed animals.[70] Further, formaldehyde is a highly reactive, rapidly metabolized chemical yielding short-lived DPCs and DNA-adducts that are amenable to rapid reversal and repair.[71,72] These observations are consistent with conventional wisdom, which has been that the expected sites of action of formaldehyde are limited to portals of entry (eg, nasal epithelium), and would not likely include distal sites, such as the bone marrow, where leukemias originate.[70,73-75] Although several possible modes of action have been postulated to explain associations between LHP cancers and formaldehyde exposure in epidemiological studies, little scientific evidence supports these hypotheses, and there is some recent evidence against them. Thus, these proposals remain speculative and continue to represent a highly controversial topic in the scientific community.

The NRC noted that little is known about the potential modes of action by which formaldehyde might cause LHP cancers, other than mutagenicity.[4] A mechanism that would explain the occurrence of LHP cancers has not been established, the epidemiological data are inconsistent, the animal data are weak, and there is a growing body of evidence that formaldehyde is not available systemically in any reactive form. Further, the lack of consistency in exposure-response relationships between several exposure metrics and the LHP cancers in the epidemiological data could reflect the absence of causal mechanisms associating these cancers with formaldehyde exposure.

## Irritation and Sensitization

As noted in the original safety assessment of formadehyde,[1] aqueous formaldehyde/formalin solutions can irritate the skin and cause contact urticaria and allergic sensitization in both occupationally and non-occupationally exposed persons. The North American Contact Dermatitis Group (NACDG) reported a 5% incidence of skin sensitization among 2,374 patients exposed to 2% formaldehyde in aqueous solution.[76] Aqueous formaldehyde solutions as low as 0.01% can elicit skin responses in some sensitized persons under occlusive conditions. Most sensitized individuals can tolerate repeated topical axillary application of products containing up to 0.003% aqueous formaldehyde solution on normal skin.[77] Cosmetic products containing 0.0005% to 0.25% formalin (0.000185%-0.0925% calculated as formaldehyde) were essentially nonirritating and non-sensitizing in 1,527 subjects in 18 studies summarized in Table 5 of the original safety assessment.[1]

Recent reviews addressing the human irritation and sensitization potential for aqueous formaldehyde/formalin solutions are consistent with the observations reported in the original assessment.[78,79]

Healthy volunteers (n=30; ≥18 years old) of either sex were exposed to 11 personal care products and 2 controls (ie, deionized water and 0.3% sodium lauryl sulfate) using an occlusive patch-testing protocol.[80] The products included 3 keratin hair straighteners containing methylene glycol (concentration not reported). All of the products were diluted to 8%, presumably with deionized water, before applying 0.2 ml of the diluted product to Webril© disks. Note that, based on the manufacturer's directions, hair straighteners are applied undiluted to the hair. The patches were applied to the skin of the upper arms of each subject and left in place for 23 hours, and removed and examined during the 24$^{th}$ hour, for 4 consecutive days. Each subject was exposed to each of the 11 products and 2 controls on patches applied to the same site of the skin each day. The specific site of application for each product/control varied from subject to subject, depending on the random assignment of each subject to one of 5 groups. None of the diluted products or the negative control elicited any more than minimal erythema throughout the study. In contrast, the positive control elicited substantial erythema.

# CLINICAL USE

## Adverse Event Reporting

***Nail Hardening Products***

A compilation of 33 customer self-reports from Internet sites and blogs of nail hardening products indicate adverse effects including skin irritation, burning sensation of nail beds and exposed skin, severe finger pain, scabbing under the nails, and drying, flaking, splitting, crumbling, or peeling of the nails.[31] Two additional reports noted that the product contained formaldehyde and has a strong odor, without noting any other adverse effects. Three reports indicated that the product contained 4%-4.5% formaldehyde.

***Hair Smoothing Products***

*Canada*
Some 50-60 individuals have reported adverse reactions to Health Canada resulting from use of hair smoothing products containing formaldehyde. These reports concerned burning eyes, nose, throat and breathing difficulties, with one report of hair loss,[41] but additional reports also were received of headache, arthritis, dizziness, epistaxis, swollen glands and numb tongue (Health Canada, personal communication).

*USA*
The Center for Research in Occupational and Environmental Toxicology (CROET) at the Oregon Health Sciences University (OHSU) has received numerous phone calls and emails from stylists from around the United States since first posting an alert on a hair product on September 16, 2011.[11] Many of the stylists reported health symptoms associated with the use of this product at work. The health symptoms reported include the following: burning of eyes and throat, watering of eyes, dry mouth, loss of smell, headache and a feeling of "grogginess," malaise, shortness of breath and breathing problems, a diagnosis of epiglottitis attributed by the stylist to their use of the product, fingertip numbness, and dermatitis. Some of these effects were also reported to have been experienced by the stylists' clients. CROET also received emails from persons who report hair loss after having the treatment. Oregon OSHA has received similar, although generally less detailed, reports from individuals who have contacted the agency as a result of recent media coverage.

The U.S. OSHA recently issued a Hazard Alert and identified safeguards that should be in place to keep formaldehyde concentrations below the U.S. OSHA occupational exposure limits.[37]

The FDA has been notified by some state and local organizations of reports from salons about problems associated with the use of Brazilian Blowout, a product used to straighten hair.[81] Complaints include eye irritation, breathing problems, and headaches. State and local organizations with authority over the operation of salons are currently investigating these reports.

The FDA adverse reporting system includes 33 adverse event reports from use of hair smoothing and straightening products from hair stylists, their customers, and individual users from 9/29/08 through 3/1/11.[82] The results clearly link the use of formaldehyde/methylene glycol-containing hair smoothing products to clinical signs and symptoms that would be expected from the vaporization and inhalation of toxic levels of this ingredient. These reported effects include irritation of the eyes, nose and throat, nasal discharge, nose bleeds, congested sinuses, hoarseness, persistent coughing, bronchitis, difficulty breathing, feeling of pressure, tightness, or pain in chest. Two reports note inhalation pneumonitis in a professional hair stylist. Other complaints include headache, dizziness, fainting, and vomiting. Reported effects potentially attributable to direct contact with these products include irritation, inflammation, or blistering of the skin, especially on the scalp, and hair loss. In addition to these 33 reports, there were 7 reports of hair loss that did not indicate whether other possible adverse effects also occurred.

# RISK ASSESSMENTS

## Carcinogenicity

In 2006, the International Agency for Research on Cancer (IARC)[83] concluded that there was *sufficient* epidemiological evidence that formaldehyde causes NPC in humans and *strong but not sufficient* evidence for a causal association between leukemia and occupational exposure to formaldehyde. They also elevated their evaluation of formaldehyde from probably carcinogenic to humans (Group 2A) to carcinogenic to humans (Group 1).

In 2009, IARC[84] updated their evaluation to conclude that there is *sufficient* evidence for a causal association between leukemia, particularly myeloid leukemia, and occupational exposure to formaldehyde. This conclusion was based primarily on:

- The statistically significant association between embalming and myeloid leukemia, including statistically significant trends for cumulative years embalming and peak formaldehyde exposure.[85]

- The levels of chromosome 7 monosomy and chromosome 8 trisomy in myeloid progenitor cells and hematological changes in formaldehyde exposed workers.[69]

The IARC Working Group was almost evenly split on the prevailing view that the evidence was sufficient for formaldehyde causing leukemia in humans.[84]

The U.S National Toxicology Program (U.S. NTP) concluded that formaldehyde is *known to be a human carcinogen* based on epidemiological reports indicating that exposures are associated with nasopharyngeal, sinonasal, and LHP cancers and data on mechanisms of carcinogenicity from laboratory studies.[86-88]

In 1991, U.S. EPA classified formaldehyde as a B1 carcinogen (ie, a probable human carcinogen), based on limited evidence in humans, and sufficient evidence in animals.[89] They estimated an upper-bound inhalation cancer unit risk of $1.6 \times 10^{-2}$ per ppm ($1.3 \times 10^{-5}$ per $\mu g/m^3$), using a linearized multistage, additional-risk procedure to extrapolate dose-response data from a chronic bioassay on male F344 rats. An upper-bound $10^{-6}$ human cancer risk would be associated with continuous inhalation of 0.06 ppb (63 ppt) formaldehyde over a lifetime, based on this unit risk.

Recently, U.S. EPA proposed to identify formaldehyde as carcinogenic to humans.[3] They proposed an upper-bound inhalation cancer unit risk for NPC, Hodgkin's lymphoma, and leukemia, combined, using log-linear modeling and extra risk procedures to extrapolate cumulative exposure estimates from the epidemiological studies.[90] The NRC agreed that the Hauptmann et al (2004) study[91] of the NCI cohort is the most appropriate for deriving cancer unit risk estimates for respiratory cancers and other solid tumors, but noted that this study is being updated.[4] The update will likely address the deaths reported to be missing from this study.[90] However, the NRC explicitly did not recommend that U.S. EPA wait until the release of the update to complete its assessment.

## Non-Cancer Effects

In 1990, U.S. EPA published a chronic reference dose (cRfD) of 0.2 mg/kg/day for oral exposure to formaldehyde, based on the results of a 2-year bioassay in rats.[89,92] Formaldehyde (methylene glycol/formaldehyde) was administered to Wistar rats (70/sex/dose) in drinking water, yielding mean doses of 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females. Severe damage to the gastric mucosa was observed at 82 and 109 mg/kg/day in males and females, respectively, but no tumors were found. The NOAEL was 15 mg/kg/day in this study.

U.S. EPA released a draft risk assessment for formaldehyde for public comment and review by the NRC.[3] They proposed a chronic reference concentration for formaldehyde exposure by inhalation, based on three "cocritical" epidemiological studies. These studies reported associations between formaldehyde exposure and increased physician-diagnosed asthma, atopy[93], and respiratory symptoms,[94] and decreased pulmonary peak expiratory flow rate[95] in residential populations, including children. The NRC agreed with U.S. EPA's assessment of a causal relationship between formaldehyde and respiratory effects, except for incident asthma based on one of the "cocritical" studies.[4,93]

# EXPOSURE ASSESSMENTS

Formaldehyde is ubiquitous in both indoor and outdoor air. Substantial sources of airborne formaldehyde include both natural and anthropogenic sources. Formaldehyde concentrations are generally greater in urban air than in agricultural areas, and greater in indoor air than in outdoor air.[3,4,83,96,97] It is estimated that the general population is exposed to an average of 0.016 to 0.032 ppm formaldehyde in indoor air.[98] In addition, formaldehyde is a natural metabolic intermediate in humans and other animals and is, thus, normally present in all tissues, cells, and bodily fluids.[96] The concentration of endogenous formaldehyde in the blood of rats, monkeys, and humans is about 0.1 mM.[99,100] Endogenous tissue formaldehyde concentrations are similar to genotoxic and cytotoxic concentrations observed in vitro.[70] In addition, formaldehyde is likely present normally in exhaled breath at concentrations of a few parts per billion (ppb).[4]

### Standards and Guidance for Formaldehyde Inhalation Exposures

**U.S. OSHA Enforceable** Standards[38]

| | |
|---|---|
| 8-hour Threshold for Hazard Communication Requirements (Threshold-TWA) | 0.1 ppm |
| 8 hour Action Level (AL-TWA) | 0.5 ppm |
| 8-hour Permissible Exposure Limit (PEL-TWA) | 0.75 ppm |
| 15-minute Short Term Exposure Limit (STEL-TWA) | 2 ppm |

The 8-hour Threshold-TWA is the time-weighted average concentration (0.1 ppm) above which employers are required to meet U.S. OSHA's hazard communication requirements.[38]

**NIOSH Recommended Exposure Limits**

| | |
|---|---|
| 10-hour Recommended Exposure Limit (REL-TWA) | 0.016 ppm |
| 15-minute Recommended Short Term Exposure Limit (REL-STEL-TWA) | 0.1 ppm |

The U.S. National Institute of Occupational Health (NIOSH) standards and recommendations were developed to protect workers primarily from irritation of the eyes, nose, throat, and respiratory system.[101]

**U.S. NAC AEGL Committee**

| | |
|---|---|
| Acute Exposure Guideline Level-1 (AEGL-1) | 0.9 ppm |

The U.S. National Advisory Committee for Acute Exposure Guideline Levels (U.S. NAC AEGL Committee) for Hazardous Substances interim acute exposure guideline level-1 (AEGL-1) for formaldehyde is defined as a concentration in air above which the general population (including susceptible individuals) could experience notable discomfort, irritation, or other adverse effects.[102]

> The AEGL-1 was based on the NOAEL for eye irritation in a study in which 5 to 28 healthy subjects previously shown to be sensitive to 1.3 or 2.2 ppm formaldehyde were exposed eye-only for 6 minutes to 0, 0.35, 0.56, 0.7, 0.9, or 1.0 ppm.[103] Subjective eye irritation responses ranged from none to slight at 0, 0.35, 0.56, 0.7 and 0.9 ppm. The 0.9 ppm AEGL-1 was applied across all acute exposure durations (10-min to 8 hours) because several studies show that there is adaptation to irritation at such concentrations and because in the absence of exercise, there are no decrements in pulmonary function parameters in healthy or asthmatic subjects inhaling 3 ppm for 3 hours.[104-106]

**ACGIH**

| | |
|---|---|
| Threshold Limit Value-Ceiling (TLV®-C) | 0.3 ppm. |

The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value-Ceiling (TLV®-C) is defined as the concentration that should not be exceeded during any part of the working exposure.[107]

**WHO**

| | |
|---|---|
| 30-minute average indoor air guideline | 0.08 ppm |

The World Health Organization (WHO) 30-minute average indoor air guideline is for the prevention of significant sensory irritation in the general population.[108] WHO notes that this guideline represents a negligible risk of upper respiratory tract cancer in humans, because it is more than an order of magnitude lower than the threshold for cytotoxic damage estimated for the nasal mucosa. Recent reviews of the relevant epidemiological and animal studies concluded that this guideline is protective against acute and chronic sensory irritation, as well as for all types of cancer (including LHP malignancies).[73,108]

## Formaldehyde Exposures During use of Nail Products

Time Weighted Average (TWA) formaldehyde exposures of nail technicians and customers were measured simultaneously, during normal operations at 30 nail salons throughout California in winter and summer.[109,110] Nail hardeners containing formaldehyde were used in some of these salons and other products containing formaldehyde resins were used in most, if not all, of the salons during the study.[109] 2,4-dinitrophenylhydrazine (DNPH)-treated silica gel absorption tubes and high-flow pumps were used to collect the samples. One sample inlet tube was placed close to the technician's breathing zone, and another close to the customer's breathing zone during the application of the nail products. A third sampler was placed in the salon about 10 feet from the work station to collect "area samples" to measure concentrations in the salon during the application of the nail products. A fourth sampler was placed inside the salon early in the morning before the salon opened, inside during the first two hours the salon was open, or outside the salon while the salon was open, to provide background data. Preliminary air samples were collected from two office buildings for comparison.

Most of the air samples were collected for approximately 4 hours, and some for about 2 hours or 8 hours.[109] The samples were analyzed using high-performance liquid chromatography (HPLC), in accordance with U.S. EPA method TO-11.[110] The measured concentrations were used to calculate 8-hour TWAs.

The authors reported 8-hour TWA formaldehyde concentrations in the breathing zones ranging from **0.0032 to 0.065 ppm** (median = 0.01 ppm; mean = 0.0187 ppm; SD = 0.0187 ppm) during the application of the nail products.[110] The corresponding area concentrations ranged from 0.0038 to 0.06 ppm (median = 0.01 ppm; mean = 0.0196 ppm; SD = 0.0195 ppm). The background concentrations, pooled, ranged from 0.0023 to 0.12 ppm (0.021 to 0.12 ppm early morning before opening; 0.014 to 0.081 ppm during first two hours after opening; 0.0023 to 0.013 ppm outside; overall: median = 0.014 ppm; mean = 0.033 ppm; SD = 0.038 ppm). The concentrations ranged from 0.015 to 0.021 ppm (mean = 0.018 ppm) in one office building, and was 0.043 ppm in the other office building. The authors did not determine the sources of the formaldehyde measured in the background samples.

Thus, the reported 8-hour TWA formaldehyde concentrations in the breathing zones during the application of the products appear to be indistinguishable from the salon area concentrations, and comparable to the background concentrations. In addition, the reported concentrations measured in the breathing zone, area, and outside background locations were uniformly lower than standards for formaldehyde, including the U.S. OSHA PEL-TWA (0.75 ppm), AL-TWA (0.5 ppm), and Threshold-TWA (0.1 ppm).

One of the 7 remaining inside background concentrations (collected during the first to hours after opening) exceeded the Threshold-TWA, and none exceeded the PEL-TWA, AL-TWA, or AEGL-1.

In another study, aluminum foil over a wooden support was used as the substrate for a nail hardening product in a chamber (1.43 $m^3$) under two conditions: "Typical:" 70 ºF, 1 air change/hour; "Elevated:" 80 ºF, 0.3 air changes per

hour.[111] Formaldehyde concentrations were measured at 5-minute intervals in the chamber air over a 10.5 hour period. The nail hardener (15 mg/cm$^2$) was painted on 70 cm$^2$ of the surface of the substrate ( >7 times the total surface of nails on the on a person's 10 fingers, assuming ~1 cm$^2$/nail). The peak chamber air concentrations (5-minute samples) were 0.15-0.6 ppm under the "Typical" conditions and 0.2 – 0.24 ppm under the "Elevated" conditions. The peak concentrations measured in the chamber in this study are not directly comparable to the OSHA/ACGIH/WHO standards and guidelines, because they are not estimates of the concentrations of formaldehyde in the breathing zones of a customer or manicurist over relevant exposure durations. In any case, the 5-minute peak concentrations in the chamber were all about an order of magnitude less than the 15-min STEL-TWA of 2 ppm.

## Formaldehyde Exposure during Use of Hair Smoothing Products

Air samples during use of hair smoothing products were measured in five separate studies. The results are summarized below and in Table 12.

Oregon OSHA and Center for Research in Occupational Toxicology (CROET) collected 15 air samples from seven beauty salons during the use of a "formaldehyde-free" hair-smoothing product.[11] They used DNPH-treated silica gel absorption tubes (SKC 226-119) and high-flow pumps, and analyzed the samples using NIOSH method 2016, which is comparable to U.S. EPA method TO-11. The concentrations of formaldehyde at the stylists' workstations ranged from **0.074 to 1.88 ppm** (median = 0.34 ppm; mean = 0.62 ppm; SD = 0.59 ppm) during sampling/exposure periods ranging from **6 to 48 minutes** (median = 19 minutes; mean = 23 minutes; SD = 12 minutes):

- 4 samples (ranging from 1.26 ppm for 34 minutes to 1.88 ppm for 26 minutes) exceeded the U.S. NAC AEGL-1 (0.9 ppm for ≥10 min).[102]
- 9 samples (0.303 to 1.88 ppm) exceeded the ACGIH TLV®-Ceiling (0.3 ppm).[107]
- All 3 samples collected for ≥30 minutes (1.26 ppm for 34 minutes, 0.34 ppm for 47 minutes, and 1.35 ppm for 48 minutes) exceeded the WHO 30-minute guideline (0.08 ppm).[108]

Further, 2 of 24 area samples collected during the procedures (**0.319 and 0.471 ppm**) exceeded the TLV®-C, and 10 of 12 area samples collected for ~30 minutes or more (eg, 0.226 ppm for 26 minutes and 0.255 ppm for 97 minutes) exceeded the WHO guideline.

Exponent® collected two 30-minute background air samples in a salon before the use of a hair smoothing product, and duplicate samples in the stylist's breathing zone, the customer's breathing zone, and within 3 feet of the customer's location during the application of the product.[112] They used U.S. EPA method TO-11 to collect and analyze the samples. The background formaldehyde concentrations were 0.024 and 0.025 ppm. The concentrations in the samples collected during the procedure ranged from **0.170 ppm for 141 minutes to 0.269 ppm for 95 minutes**. All of these concentrations were from 57% to 90% of the ACGIH TLV®-C (0.3 ppm), and all exceeded the WHO 30-minute guideline (0.08 ppm).

The Tennessee Occupational Safety and Health Administration (Tennessee OSHA) conducted an inspection of a salon, including the collection and analysis of air samples.[113] They used DNPH-treated silica gel absorption tubes (XAD-2) and high-flow pumps (SKC AirCheck 2000) to collect, apparently, one air sample every 15 minutes for 75 minutes during the use of the product. The analytical method was not specified. The 15-minute concentrations ranged from **0.3 to 1.07 ppm**. One of these values is equal to the TLV®-C (0.3 ppm), and the 4 others exceeded the TLV®-C (0.3 ppm) by up to nearly 4-fold. The highest value (1.07 ppm) exceeds the U.S. NAC AEGL-1 (0.9 ppm). In addition, the 75-minute TWA calculated from the reported series of 15-minute concentrations is 0.558 ppm, which is approximately 7-times greater than the WHO 30-minute guideline (0.08 ppm).

The Professional Keratin Smoothing Council (PKSC) submitted the results of the analysis of 15-minute air samples collected during the blow-drying or flat-ironing steps of 4 hair-smoothing treatments.[13,114] They used Sep-Pak® DNPH-Silica Cartridges to collect the samples. No further details were provided about the methodology. Formaldehyde was not detected (reporting limit 0.0082 ppm) in one of the samples collected during blow drying, and was not included in the PKSC summary table, presumably because of technical difficulties encountered with this sample. The 15-minute concentrations in the 7 remaining samples ranged from **0.761 to 1.71 ppm**. None of

these samples exceeded the 15-minute STEL-TWA. However, all of the samples exceeded the ACGIH TLV®-C (0.3 ppm) by 2.5 to 5.7-fold, and all but one of them exceeded the U.S. NAC AEGL-1 (0.9 ppm) by 1.3 to 1.9 fold. TWAs (30-minute) calculated from each complete 15-minute sample pairs (ie, blow drying plus flat ironing) ranged from 0.996 to 1.69 ppm, exceeding the WHO 30-minute guideline (0.08 ppm) by 12 to 21-times.

The PKSC submitted the results of air samples collected to estimate the stylist's and customer's inhalation exposures in a beauty salon during hair-smoothing treatments conducted on two separate occasions.[13,115] They used Sep-Pak® DNPH-Silica Cartridges to collect the samples. No further details were provided. The results ranged from **0.189 ppm for 117 minutes to 0.395 ppm for 86 minutes**. The concentrations in two of the samples (customer exposure to 0.355 ppm for 117 minutes; stylist exposure to 0.395 ppm for 86 minutes) exceeded the ACGIH TLV®-C (0.3 ppm). All of the air samples exceeded the WHO 30-minute guideline (0.08 ppm) by 2.4 to 5 times.

In another study, Exponent® collected 63 air samples at 6 salons where hair-smoothing treatments were performed.[116,117] These included 6 area (background) samples collected before any hair-smoothing procedures were conducted, and 35 samples collected in the stylists' breathing zones during a total of 9 treatments. An additional 22 area samples were collected in the salons within 5 feet of the stylists during and after the procedures. They used DNPH-treated silica gel absorption tubes (SKC 226-119) and followed NIOSH method 2016 to collect and analyze the samples. Following is a summary of the results:

- Concentrations in the 6 background samples ranged from 0.0068 to 0.032 ppm.

- Concentrations in the other 22 area samples ranged from <0.005 ppm for 45 minutes to 0.14 ppm for 73 minutes. The 3 highest area concentrations (ranging from 0.084 ppm for 69 minutes to 0.14 ppm for 73 minutes) were collected during the treatments, and exceeded the WHO 30-minute guideline (0.08 ppm).

- Calculated 8-hour TWAs ranged from 0.02 ppm to 0.08 ppm. The highest of these is equal to the WHO 30-minute guideline.

- Concentrations in 9 samples collected in the breathing zones during the procedures (including application of the product, blow drying and flat ironing) ranged from 0.11 ppm for 63 minutes to 0.33 ppm for 73 minutes. The highest concentration (0.33 ppm) exceeded the ACGIH TLV®-C (0.3 ppm), and all of them exceeded the WHO 30-minute guideline (0.08 ppm) by up to 4 fold.

- Concentrations in the 26 samples collected in the breathing zones during each of the separate steps the procedures ranged from **0.041 ppm for 43 minutes** (during flat ironing) to **0.76 ppm for 17 minutes** (during blow drying). The 4 highest concentrations (ranging from 0.66 for 20 minutes to 0.76 ppm for 17 minutes) were 73% to 84% of the U.S. NAC AEGL-1 (0.9 ppm). Concentrations in 9 of the 26 samples (ranging from 0.31 ppm for 32 minutes to 0.76 for 17 minutes) exceeded the ACGIH TLV®-C (0.3 ppm) by up to 2.5 fold. Concentrations in 6 of the 10 samples collected for 30 minutes or more during each step of the treatments (ranging from 0.084 ppm for 31 minutes to 0.31 ppm for 32 minutes) exceeded the WHO 30-minute guideline (0.08 ppm) by up to 4 times.

### *Simulated Use; Calculated Formaldehyde Levels*

Berkeley Analytical placed 0.0946 grams of a hair smoothing product in a glass Petri dish, placed the dish in a small-scale, ventilated environmental chamber (0.067 $m^3$), and followed ASTM D 5116 procedures for measuring organic emissions from indoor materials and products.[118,119] They collected three consecutive 1-hour air samples from the chamber (1 air change/hour), at room temperature (73.4 ºF), using Sep-Pak XPoSure samplers. They reported emissions factors for formaldehyde ranging from 1,020 µg/gram-hour for the first hour to 1,670 µg/gram-hour for the third hour. Indoor Environmental Engineering calculated formaldehyde concentrations in a hypothetical hair salon (240 $ft^2$; 8-ft ceiling) from single 90-minute emissions of formaldehyde from the hair smoothing product. They conservatively assumed a 1,020 µg/gram-hour emission rate at room temperature, likely underestimating the emissions during actual use.[34] The emission rates are most probably much higher when the product is heated (eg, during blow-drying and flat-ironing). They modeled TWA exposure concentrations for the customer (110 minutes) and the stylist (8 hours), assuming 3 outdoor air ventilation rates (0.13 to 0.6 $ft^3$/min-$ft^2$) and three different amounts

of the product applied the customer's hair (12.6 to 37.8 grams). The amounts were selected from recommendations provided in the manufacturer's training video for using the product on short, medium and long hair.

The 110-minute formaldehyde concentrations ranged from 0.033 ppm (12.6 grams product; 0.6 $ft^3/min\text{-}ft^2$) to 0.269 ppm (37.8 grams product; 0.6 $ft^3/min\text{-}ft^2$). Two of the three 110-minute estimates assuming 25.2 grams of product (0.096 to 0.18 ppm at 0.38 and 0.13 $ft^3/min\text{-}ft^2$, respectively) and all of the estimates assuming 37.8 grams (0.098 to 0.269 ppm), exceeded the WHO 30-minute guideline (0.08 ppm). The highest estimate (0.269 ppm) was about 90% of the ACGIH TLV®-C (0.3 ppm). In addition, the highest estimated 8-hour TWA was 0.108 ppm (37.8 grams; 0.13 $ft^3/min\text{-}ft^2$), which exceeds the U.S. OSHA 8-hour Threshold-TWA (0.1 ppm).

## DISCUSSION

Based on the available data, the CIR Expert Panel (Panel) considered that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin† concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair smoothing products. This is a final amended safety assessment.

The Panel emphasized that a large body of data has demonstrated that formaldehyde gas exposure can cause nasopharyngeal cancers (NPCs). While debate is ongoing regarding the dose-response relationship for the induction of NPCs, the Panel continues to believe that formaldehyde gas can produce such cancers at high doses. Epidemiology studies have suggested a weak association between exposure to formaldehyde and lymphohematopoietic (LHP) cancers. The reported association of formaldehyde exposure with LHP cancers is just that, an association, and the Panel is not aware of a plausible mechanism by which formaldehyde exposure could be causally linked to LHP tumors. Based on the testicular effects observed in rats exposed to formaldehyde, the CIR Panel acknowledged that a mechanism of action by which formaldehyde might cause the testicular effects is not known and these effects may be secondary to local effects, such as irritation and inflammation, and stress at high doses.

The Nail Manufacturers Council, the Professional Keratin Smoothing Council (PKSC), the American Chemistry Council, the Personal Care Products Council, and one individual provided new data and comments. After reviewing the comments and additional data, the Panel determined that the data were sufficient to support the safety of these ingredients in nail hardeners.

The additional data confirmed the current use concentration of formaldehyde/methylene glycol in the 1 – 2% range in nail hardeners (one product tested had a value of 2.2%). Given the rapid reaction on the nail surface and the use of nail hardeners at room temperature, the Panel did not consider that formaldehyde/methylene glycol at 1 – 2% in nail hardeners would present a risk of sensory irritation to the eyes, nose, or throat of users. The Panel noted that the present practices of use of nail hardeners include instructions that cautioned users to limit application of the material to the top surface of the nail only, to allow it to dry fully, and to not get the material on the skin.

The Panel noted that the OSHA occupational safety limits include a time-weighted average permissible exposure level of 0.75 ppm for a work day and a short-term exposure limit of 2 ppm. Air monitoring and medical exams are triggered when formaldehyde concentrations in workplace air exceed 0.5 ppm averaged over an 8-hour shift, and ventilation and training when concentrations exceed 0.75 ppm averaged over 8 hours or 2 ppm averaged over 15 minutes. Formaldehyde must be listed in a company's MSDS if formaldehyde is present at 0.1% or more, or if the product releases formaldehyde gas above 0.1 ppm.

While such requirements are mandated by OSHA, the Panel remained concerned about adverse reports of sensory irritation consistent with measured air levels of formaldehyde in salons using hair smoothing products (a.k.a. hair straightening products) containing formaldehyde/methylene glycol. Because the use of these products involves the application of heat, the Panel remained concerned about the amounts of formaldehyde vapor that can be released. The reported levels of formaldehyde gas measured in the air around salon work stations can be below occupational exposure standards and guidelines, but also may be at or only marginally below occupational exposure standards and above indoor air quality guidelines. The Panel noted that the PKSC suggested that these products are

manufactured with the expectation that adequate ventilation would be provided during use; ie, safe use requires adequate ventilation. OSHA and other inspections, however, reported a range of ventilation controls, many of which were inadequate.

Additional use studies were done on behalf of the PKSC to demonstrate that exposure to formaldehyde could be minimized with proper procedures and use of personal ventilation devices. The Panel acknowledged that formaldehyde levels in air samples were lower in the most recent data compared to data submitted earlier, but proper safety procedures, including positioning of personal ventilation devices, were not uniformly followed.
In concept, therefore, limits on the concentration of formaldehyde/methylene glycol in hair smoothing products, control of the amount of product applied, use of lower temperatures, and approaches to mandate adequate ventilation, are among the steps that could be taken to ensure that these products would be used safely in the future. However, in the present practices of use and concentration (on the order of 10% formaldehyde/methylene glycol, blow drying and heating up to 450 $^{o}$F with a flat iron, inadequate ventilation, resulting in many reports of adverse effects), hair smoothing products containing formaldehyde and methylene glycol are unsafe.

The Panel adopted a suggestion to include limits for formalin concentration because formalin is what formulators actually add to cosmetic products. Formalin is an aqueous solution typically containing 37% (w/w) formaldehyde. Formalin contains both formaldehyde and methylene glycol because of the equilibrium between formaldehyde and methylene glycol in aqueous solution.

While retaining the concept that formaldehyde and methylene glycol should be used only at the minimal effective concentration, the Panel stated that in no case should the formalin concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. While these numbers appear to be disparate, they are not. The value of 0.074 % (w/w) of formaldehyde simply reflects that formalin typically contains 37% formaldehyde (0.2% (w/w) formalin multiplied by 0.37 = 0.074% (w/w) formaldehyde). The value of 0.118% (w/w) for methylene glycol simply reflects the difference in molecular weight between formaldehyde and methylene glycol.

The Panel recognized that the most commonly used analytical methods for the detection and measurement of formaldehyde are not specific for non-hydrated formaldehyde, but can accurately indicate the presence and quantity of formaldehyde equivalents. A typical method, for example, can detect formaldehyde equivalents in a formulation, or released into the air, via a two stage process: 1) derivatization of a sample with a hydrazine (which reacts with formaldehyde or methylene glycol, in a formulation sample or in an air sample), and 2) detection and measurement of the resultant hydrazone (ie, the reaction product of the hydrazine and formaldehyde) with a diode array, after separation on a column (eg, high performance liquid chromatography separation followed by ultraviolet/visible light (UV/Vis) detection).

While other formaldehyde/methylene analytical techniques are known, such as nuclear magnetic resonance (NMR) spectrometry, the Panel found that the methodology used by OSHA and FDA produces consistent results that are directly and meaningfully comparable to regulatory standards and guidelines. As the conditions under which formaldehyde is measured in products can affect the results, the method used to measure formaldehyde in products should be appropriate for the conditions, such as temperature and pH, under which the product is used.

The Panel reasoned that the term “formaldehyde equivalents” best captures the idea that methylene glycol is continuously converted to formaldehyde, and vice versa, even at equilibrium, which can be easily shifted by heating, drying, and other conditions to increase the amount of formaldehyde. Any other term would not distinguish the rapid, reversible formaldehyde/methylene glycol equilibrium from the slow, irreversible release of formaldehyde resulting from so-called formaldehyde releaser preservatives (eg, diazolidinyl urea). Formaldehyde releaser preservatives are not addressed in this safety assessment. The formaldehyde releasers may continue to be safely used in cosmetics at the levels established in their individual CIR safety assessments.

## CONCLUSION

The CIR Expert Panel concluded that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin[†] concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair smoothing products (a.k.a. hair straightening products).

[†]Formalin is an aqueous solution wherein formaldehyde (gas) has been added to water to a saturation point, which is typically 37% formaldehyde (w/w). Because of the equilibrium between formaldehyde and methylene glycol in aqueous solution, formalin is composed of both formaldehyde and methylene glycol.

# TABLES AND FIGURE

**Table 1. Frequency and Concentration of Use Table Formaldehyde, Formalin and Methylene glycol**

| | *No. of Uses (2010)* [15] | *Conc. of Use (2011) (%)* [16-19] | *No. of Uses (2010)* [15] | *Conc. of Use (2011) (%)* [16-19] |
|---|---|---|---|---|
| | **formaldehyde (and formaldehyde solution (formalin))**[a] | | **methylene glycol**[b] | |
| **Totals**[c] | **77** | **0.04 – 2.2** | **NR**[d] | **0.8-3.5** |
| ***Duration of Use*** | | | | |
| *Leave-On* | *33* | *0.056 – 2.2* | *NR* | *0.8-3.5* |
| *Rinse Off* | *44* | *0.04* | *NR* | *NR* |
| ***Product Category*** | | | | |
| Bath oils, tablets and salts | 1 | NR | NR | NR |
| Bubble baths | 1 | NR | NR | NR |
| Hair conditioner | 16 | NR | NR | NR |
| Permanent waves | 2 | NR | NR | NR |
| Shampoos (non-coloring) | 13 | 0.04 | NR | NR |
| Hair grooming aids | 6 | 0.056 | NR | NR |
| Other hair preparation | 7 | NR | NR | NR |
| Other hair coloring preparation | 2 | NR | NR | NR |
| Manicure basecoats and undercoats | 2 | NR | NR | NR |
| Nail Hardeners | 6 | <0.5-2.2 | NR | <0.8-3.5 |
| Bath soaps and detergents | 7 | NR | NR | NR |
| Other personal care products | 2 | NR | NR | NR |
| Shaving cream | 1 | NR | NR | NR |
| Depilatories | 2 | NR | NR | NR |
| Body and hand (excl. shave prep.) | 2 | NR | NR | NR |
| Skin moisturizing preparations | 1 | NR | NR | NR |
| Paste masks (mud packs) | 1 | NR | NR | NR |
| Other skin care preparations | 5 | NR | NR | NR |

[a]Reported as formaldehyde
[b]Calculated as methylene glycol
[c]Totals = Rinse-off + Leave-on Product Uses
[d]NR = Not Reported

**Table 2. List of ingredients in Brazilian Blowout from the Brazilian Blowout MSDS dated 10/26/10**

| Ingredient | Percentage |
|---|---|
| Water | ≤85% |
| Methylene glycol | <5% |
| Behenyl methylammonium methosulfate/N-hexadecanol/butylene glycol | ≤5% |
| Isoparaffin | ≤3% |
| Cetrimonium chloride | ≤2% |
| Petrolatum | ≤1% |
| Hypnea musciformis extract/Gellidiela acerosa extract/Sargassum filipendula extract/sorbitol | ≤1% |
| Theobroma grandiflorum seed butter (cupuacu butter) | ≤0.5% |
| Panthenol | ≤0.25% |
| Hydrolyzed keratin | ≤1% |
| Fragrance (parfum) | ≤1% |
| Methylchloroisothiazolinone | ≤0.1% |
| Methylisothiazolinone | ≤0.1% |

**Table 3. Skin irritancy/sensitization studies of formaldehyde/methylene glycol in test animals**

| Species (n) | Concentrations; volume; duration | Results | Reference |
|---|---|---|---|
| | **Multiple dose studies** | | |
| Hartley guinea pigs (n = 5/group) | 1%, 3%, 10% formalin; 100 µl/d,10 days | Dose-dependent increase in skin-fold thickness was observed, with shorter latencies at higher concentrations; e.g., erythema on treatment day 6 for 1%, day 5 for 3%, and day 2 for 10% formalin. | [120] |
| English smooth-haired guinea pigs (n = 4 or 8 males/group) | **Induction, Dermal:**<br>(a) 100% formalin; 100 µl/d, 2 days<br>(b) 50% formalin w/50% adjuvant; 200 µl/d, 1 day<br>(c) 0.13, 1.3, 13, 54, 100% formalin; 25 µl/d, 1day<br>**Induction, Inhalation:**<br>(a) 6, 10 ppm; 6 h/d, 5 days<br>(b) 10 ppm; 8h/d, 5 days<br>**Challenge, Dermal:**<br>5.4% formalin; 20 µl/d, 1 day | Dose-dependent contact sensitivity was observed in all of the animals exposed dermally during the induction phase and challenged on day 7 of the experiment. Two of the 4 guinea pigs challenged on day 31exhibited signs of contact sensitivity (mild) after inhalation of 10 ppm, 8 h/d for 5 days. No contact sensitivity was observed in the other inhalation groups or in any of the control groups. | [121] |
| Wistar and BN rats (n = 4 females/group) | 2.5, 5, 10% formalin in 4:1 acetone/raffinated olive oil; 75 µl/d, 3 days | Increase in the weights of the lymph nodes and dose-related increase in the proliferation of paracortical cells were observed in both strains in response to 5% and 10% formalin (1.9% and 3.7% formaldehyde equivalents) in a local lymph node assay (LLNA). No statistically significant increase in serum IgE concentrations were observed in BN rats (high IgE responders) in a parallel experiment. | [122] |

**Table 4. Genotoxicity inhalation studies of formaldehyde/methylene glycol in test animals**

| Species (n) | Concentrations; duration | Results | Reference |
|---|---|---|---|
| | | **Multiple dose studies** | |
| Sprague-Dawley rats (n = 10 males/group) | 0, 5, 10 ppm; 6 h/d, 5 d/wk, 2 weeks | Statistically significant, dose-dependent increases in Comet Olive tail moments were observed in blood lymphocytes, liver cells, and lung tissue.<br><br>**Comment:** A critical review noted that formaldehyde-induced formation of DNA-protein crosslinks (DPCs) and DNA-DNA crosslinks (DDCs) in the cells should have decreased, rather than increased, DNA migration in these assays. | [52,53,123] |
| F344/DuCrl rats (n = 6 males/group) | 0, 0.5, 1, 2, 6, 10, 15 ppm; 6 h/d, 5 d/wk, 4 weeks | No statistically significant differences were found between the exposed and negative control groups in Comet tail moment or intensity, or sister chromatid exchange (SCE) and micronuclei (MN) frequencies in peripheral blood samples. The results of the Comet assay were negative even after irradiating the blood samples to increase sensitivity for detecting DNA-protein crosslinks (DPCs). Statistically significant effects were observed in the positive controls (ie, orally administered methyl methanesulfonate or cyclophosphamide), demonstrating the sensitivity of the tests. | [54] |

**Table 5. Genotoxicity inhalation studies of formaldehyde/methylene glycol in human subjects**

| Subjects (n) | Concentrations; duration | Results | Reference |
|---|---|---|---|
| (a) Workers at a formaldehyde manufacturing plant (n = 10)<br>(b) Waiters (n = 16)<br>(c) Students (n = 23) | (a) 0.80 ± 0.23 ppm 8-h TWA, 1.38 ppm Ceiling; average 8.6 years, range 1 to 15 years<br>(b) 0.09 ± 0.05 ppm 5-h TWA; 12 weeks<br>(c) 0.009 ppm 8-h TWA; not reported | Statistically significant increases in mononucleus (MN) and sister chromatid exchange (SCE) frequencies were found in nasal mucosa cells of the workers compared to student controls. The MN and SCE frequencies in nasal mucosa cells from the waiters were not different from the controls. | [58] |
| (a) Workers at two plywood factories (n = 151)<br>(b) Workers at a machine manufacturing facility (n = 112) | (a) 0.08-6.42 ppm TWA<br>(b) <0.008 ppm TWA | Exposure-related, statistically significant increases were found in Comet Olive tail moments and lengths and MN frequencies in lymphocytes from the plywood-manufacturing workers compared to controls (ie, machine-manufacturing workers). | [59] |
| (a) Pathology and anatomy laboratory workers (n = 59)<br>(b) Individuals matched for gender, age, smoking (n = 37) | (a) 2 ppm 15-min TWA (range <0.1-20.4 ppm), 0.1 ppm 8-h TWA (range <0.1-0.7 ppm)<br>(b) Not determined | No increase in DNA damage was observed in the lymphocytes of the pathologists/anatomists after one day of exposure, using a chemiluminescence microplate assay. Statistically significant increases in mono- and bi-nucleated lymphocyte frequencies were found in pathologists/anatomists compared to the controls using cytokinesis-blocked micronucleus (CBMN) & fluorescence in-situ hybridization (FISH) assay. No statistically significant differences were observed in the frequencies of centromeric or acentromeric MN. The authors suggested that the results are attributable to an aneugenic rather than clastogenic mode of action. | [56] |
| Volunteers (n = 10 women, 11 men) | 0.15 to 0.5 ppm (concentration randomly assigned to each subject each day) w/ four 15-min 1-ppm peaks & three 15-min bicycling exercises during each exposure; 4 h/d, 10 days (Cumulative: 13.5 ppm-hour, 10 days) | A statistically significant decrease in MN frequency was observed in buccal mucosal cells collected 21days after the end of the exposure period compared with the control samples collected from the subjects 1 week before exposure. MN frequencies in samples collected immediately, 7 days, or 14 days after exposure did not differ from the control samples. | [57] |
| (a) Hospital pathological anatomy laboratory workers (n = 30)<br>(b) Matched administrative personnel in the hospitals (n = 30) | (a) 0.44 ± 0.08 ppm mean 8-h TWA (range 0.04−1.58 ppm)<br>(b) Not determined | Statistically significant increase in MN and SCE frequencies and Comet tail lengths were observed in lymphocytes collected from laboratory workers (employment duration averaging 11±7 years, ranging from 0.5 to 27 years) compared with controls. A statistically significant, positive correlation between exposure and both MN frequency and Comet tail length was found in the lymphocytes of the laboratory workers. | [55] |

**Table 5. Genotoxicity inhalation studies of formaldehyde/methylene glycol in human subjects**

| Subjects (n) | Concentrations; duration | Results | Reference |
|---|---|---|---|
| Healthy, non-smoking male volunteers (n = 41); 12 groups (n = 2 to 4/group) | Each subject exposed once to 0, 0.3 w/ four 15-min 0.6-ppm peaks, 0.4 w/ four 0.8 ppm peaks, and 0.5 ppm; 4 h/d, 5 days (subjects performed four 15-min bicycling exercises during each exposure period, including 2 during peaks) | A small but statistically significant increase in Comet tail intensity was observed in lymphocytes after the 5-day exposure period compared to the values determined before exposure. The authors concluded that this finding was not biologically significant, because formaldehyde-induced DPCs would be expected to decrease, not increase, Comet tail intensity. No statistically significant differences were found in Comet tail moments or SCE and MN frequencies in lymphocytes, MN frequencies in nasal epithelial cells, or biologically significant changes in gene expression in nasal biopsies collected after exposure compared with those collected before exposure. | 60 |

**Table 6. Nasal tissue studies of formaldehyde/methylene glycol in test animals**

| Species (n) | Concentrations; duration(s) | Results | Reference |
|---|---|---|---|
| | | **Multiple dose studies** | |
| F344 CDF(F344)/CrlBr rats (n = 6 males/group) | 0, 0.7, 2, 6, 10, 15 ppm; 6 h/d, 5d/wk, 1, 4, 9, 42 days (short-term) or 3, 6, 12, 18, 24 months (long-term) | Statistically significant increases in nasal cell proliferation were found only at ≥6.0 ppm (short-term) and ≥10.0 ppm (long-term).<br><br>**Comment:** The authors and their co-workers interpreted these data to indicate that the dose-response curve is non-monotonic (ie, highly-nonlinear), because cell proliferation was diminished at lower doses and elevated at the higher, cytotoxic doses. This view is consistent with the hypothesis that formaldehyde exposure must be sufficient to stimulate regenerative cell proliferation, thereby increasing the likelihood that mutations that would otherwise be repaired will become permanent, and could then lead to tumor formation. Others have disputed this interpretation, because of the considerable uncertainty and variability in the data. | 64-66,124,125 |
| F344/CrlBR (n = 8 males/group) | 0, 0.7, 2, 6, 10, 15 ppm; 6 h/d, 1,4,13 weeks | Transcriptional and histological changes at ≥6 ppm corresponded to doses for which pharmacokinetic modeling predicted substantial decrease in free glutathione (GSH) and increase in methylene glycol in nasal tissue.<br><br>**Comment:** The authors concluded that formaldehyde exposure below 1 to 2 ppm in air would not perturb formaldehyde homeostasis in epithelial cells or elevate the risk of cancer in any tissue, consistent with a threshold for tissue responses and carcinogenicity. | 126 |
| F-344/NCrl rats (n = 5 males/group) | 0, 0.7, 2, 6, 10, 15 ppm; 6 h/d, 13 weeks | Mutation levels were not elevated above the low spontaneous background levels, even in the rats exposed to 15 ppm formaldehyde, and showed no dose-related increases. Bromodeoxyuridine (BrdU) incorporation increased with dose and was statistically significantly elevated in the rats exposed to either 10 ppm or 15 ppm formaldehyde.<br><br>**Comment:** The results support the view that cytotoxicity-induced cell proliferation (CICP) plays a pivotal role in the formation of NPCs in rats and, thus, formaldehyde-induced carcinogenicity is largely a threshold effect. | 62 |
| F344 (n = 10 to 30 males/group) | 0.7, 2, 5.8, 9.1, 5.2 ppm; 6 hours | Formation of endogenous DNA adducts did not change in a dose-related manner in nasal epithelium. In contrast, the formation of exogenous adducts was highly non-linear, increasing 286-fold with a 21.7-fold increase in the exposure concentration. About 1% and 3% of the total number of adducts (endogenous plus exogenous) were exogenous adducts at 0.7 ppm and 2 ppm, respectively. | 61 |
| Cynomolgus macaques (n = 8 males) | 1.9, 6.1 ppm; 6 h/d, 2 days | Endogenous and exogenous DNA adducts were detected in the nasal tissues at both exposure concentrations.<br><br>**Comment:** The monkeys exposed to 6.1 ppm exhibited greater numbers of endogenous adducts and lower numbers of exogenous adducts in nasal tissues, compared with rats exposed to 5.8 ppm. Based on these results, the authors' suggested that the percentage of exogenous adducts would be lower in primates than in rats at equivalent exposure concentrations. | 63,68 |

**Table 7. Epidemiological studies of formaldehyde/methylene glycol and nasopharyngeal cancers**

| Study design; subjects (n) | Exposure metrics | Results | Reference |
|---|---|---|---|
| Retrospective Cohort mortality; Men employed after 1937 at six British factories where formaldehyde was produced or used, followed through 2000 (n = 14,014), compared with the general population | (a) Background: <0.1 ppm<br>(b) Low: 0.1 to 0.5 ppm<br>(c) Moderate: 0.6 to 2.0 ppm<br>(d) High: >2.0 ppm | One nasopharyngeal cancer (NPC) mortality was identified among the factory workers, which included 3,991 workers exposed to >2 ppm. The single NPC case worked in a job with low exposure; two NPC cases were expected. Two sinonasal cancer deaths were identified, both having high exposures; 2.3 cases were expected. Fifteen pharyngeal tumor deaths were observed; 9.7 cases were expected. | 127,128 |
| Retrospective cohort mortality; Textile workers (82% female) employed after 1955 at 3 U.S. garment facilities, followed through 1998 (n = 11,039), compared with U.S. and local populations | (a) 8-h TWA (across all departments and plants) mean 0.15 ppm, range 0.09 to 0.2 ppm<br>(b) Age at first exposure: median 26.2, range 15.2–79.8 years<br>(c) Duration: <3, 3 to 9, ≥10 years<br>(d) Time since first exposure: <10, 10 to 19, ≥20 years<br>(e) Year first exposed: <1963, 1963 to 1970, ≥ 1971 | No cases of NPC or nasal cancers were found; 1 case was expected. | 128,129 |
| Retrospective cohort mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants (NCI cohort; Plants #1-#10) and followed through 1994 (n = 25,619) | (a) Average intensity: 0, ≤0.5, 0.5 to <1.0, ≥1.0 ppm<br>(b) Cumulative: 0, >0 to <1.5, 1.5 to <5.5, ≥5.5 ppm-years<br>(c) Duration: 0, >0 to <5, 5 to <15, ≥15 years<br>(d) Ever vs. never exposed<br>(e) Peak: 0, >0 to <2.0, 2.0 to <4.0, or ≥ 4.0 ppm | Nine deaths from NPC were identified in this cohort, including 7 classified as "ever exposed" and 2 as "never exposed." The highest relative risk (RR) estimates were 4.14 for ≥5.5 ppm-years cumulative exposure and 4.18 for ≥15 years exposure duration. Although confidence limits were not specified, the authors' footnotes indicate that they included 1 for these RR estimates. However, statistically significant dose-response trends were apparent for both peak exposure and cumulative exposure.<br><br>**Comment:** Other researchers have demonstrated critical weaknesses in the model used in this study, including instability problems related to the data from Plant #1. | 91,130-132 |
| Retrospective cohort mortality; Workers employed in a plastics-manufacturing plant in Wallingford CT (NCI cohort; Plant #1) from 1941 to 1984 followed through 1998 (n = 7,328) compared with general population of 2 CT counties | (a) Average intensity: 0 to <0.03, 0.03 to 0.159, ≥0.16<br>(b) Cumulative: 0 to <0.004, 0.004 to 0.219, ≥0.22 ppm-years<br>(c) Duration: 0 to <1, 1 to 9, ≥ 10 years<br>(d) Duration exposed to >0.2 ppm: 0, 0 to <1, 1 to 9, ≥10 years<br>(e) Short-term (<1 year) vs. long-term (>1 year) worker | Seven NPC cases were identified in this cohort, including 6 cases specifically identified as NPC and 1 case of pharyngeal cancer that was not identified specifically as NPC in the records. Several formaldehyde exposure metrics were associated with NPC for Plant #1, including "ever exposed," exposure duration ≥10 years, and cumulative exposure ≥0.22 ppm-years. The standardized mortality ratios (SMRs) estimated for these metrics were 6.03, 12.46, and 7.51, respectively, all with confidence limits >1.<br><br>**Comment:** The authors suggested that their findings do not support a causal relationship between formaldehyde exposure and NPC mortality because elevated risks were seen in both short-term (<1 year; 4 cases) and long-term workers (3 cases), 5 NPC cases worked <5 years at the plant, the NPC cases among the long-term workers (>1 year) had relatively low average-intensity exposures (0.03-0.60 ppm), and the NPC deaths were concentrated among workers hired during 1947-1956. | 133 |
| Retrospective cohort mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants (NCI cohort; Plants #1-#10) and followed through 1994 (n = 25,619 | (a) Average intensity: <1.046, 1.046 to 1.177, ≥1.178 ppm<br>(b) Cumulative: <0.734, 0.734 to 10.150, ≥10.151 ppm-years<br>(c) Duration: <0.617, 0.617 to 2.258, ≥2.259 years<br>(d) Highest peak: >0 to 1.9, 2.0 to 3.9, ≥4.0 | Six of 10 NPC deaths (ie, identified specifically as NPC) in this cohort were associated specifically with employment at Plant #1, the remaining 4 cases distributed among 4 of the other 9 plants studied. A regional rate-based SMR of 10.32 (95% CI: 3.79-22.47) was estimated for exposed workers at Plant #1, compared to 0.65 (95% CI: 0.08 to 2.33) for exposed workers at Plants #2 through #10 combined. The statistically significant peak exposure-response relationship in the cohort was driven by excess NPC risk associated with the highest peak exposure category (≥4 ppm) at Plant #1. None of the exposure-response relationships for any of the four exposure metrics were statistically significant for Plants #2 through #10, combined. The authors concluded that the suggestion of a causal relationship between | 134 |

**Table 7. Epidemiological studies of formaldehyde/methylene glycol and nasopharyngeal cancers**

| Study design; subjects (n) | Exposure metrics | Results | Reference |
|---|---|---|---|
| | ppm | formaldehyde exposure and NPC mortality in previous studies was based entirely on anomalous findings at Plant #1. | |
| Retrospective cohort mortality; Workers employed in a plastics-manufacturing plant in Wallingford CT (NCI cohort; Plant #1) from 1941 to 1984 (n = 7,345) followed through 2003, nested case-control and comparison with general populations of U.S. and local counties | (a) Average intensity: 0 to <0.03, 0.03 to 0.159, ≥0.16<br>(b) Cumulative: 0 to <0.004, 0.004 to 0.219, ≥0.22 ppm-years<br>(c) Duration: 0 to <1, 1 to 9, ≥10 ppm<br>(d) Exposed vs. unexposed | SMRs of 4.43 (95% CI: 1.78-9.13) and 4.34 (95% CI: 1.74-8.94) were calculated for the 7 NPC mortalities among the exposed Plant #1 workers compared with local and U.S. rates, respectively. Four of the 7 NPC cases also held silver-smithing jobs, and 5 of the 7 NPC cases held silver-smithing or other metal-working jobs, and this type of work was relatively rare in the remaining study population. The authors noted possible exposures to several suspected risk factors for upper respiratory system cancer (eg, sulfuric acid mists, mineral acid, metal dusts and heat) associated with this type of work. | [135] |
| Nested case-control; Deceased embalmers and funeral directors (n = 6,808) | (a) Average intensity while embalming: 0, >0 to 1.4, >1.4 to 1.9, >1.9 ppm<br>(b) Cumulative: 0, >0 to 4058, >4058 to 9253, >9253 ppm-hours<br>(c) Duration in jobs involving embalming: 0, >0 to 20, >20 to 34, >34 years<br>(d) Ever vs. never embalming<br>(e) Lifetime 8-h TWA: 0, >0 to 0.1, >0.1 to 0.18, >0.18 ppm<br>(f) Number of embalmings conducted: 0, >0 to 1422, >1422 to 9253, >9253<br>(g) Peak: 0, >0 to 7, >7 to 9.3, >9.3 ppm | Four cases of NPC were identified, only two of which had “ever embalmed” (Odds ratio = 0.1; 95% CI: 0.01-1.2). Exposure estimates for these 2 cases were indistinguishable from controls. | [85] |

## Table 8. Comparative tissue studies of formaldehyde/methylene glycol in test animals

| Species (n) | Concentration(s); duration(s) | Results | Reference |
|---|---|---|---|
| **Multiple dose studies** | | | |
| F344 (n = 30 males) | 10 ppm; 6 h/d, 1 or 5 days | Exogenous formaldehyde-induced DNA monoadducts and DNA-DNA crosslinks (DDCs) were found exclusively in the nasal tissues after exposure. No exogenous products were detected in any other tissue even though, for example, the analytical method can detect ~3 monoadducts/$10^9$ deoxyguanosine (dG). This detection limit is ~30 times less than the endogenous monoadducts/$10^9$ dG measured in white blood cells (on-column detection limits ~240 and 60 amol for monoadducts and crosslinks, respectively).<br><br>Endogenous products were found in all of the tissues examined, including blood and bone marrow. The levels of endogenous products were comparable across all tissues examined.<br><br>The authors concluded:<br>(1) Neither formaldehyde nor methylene glycol from formaldehyde reaches sites distant from the portal of entry, even when inhaled at high concentrations known to stimulate nasal epithelial cell proliferation and cause nasal tumors in rats.<br>(2) Genotoxic effects of formaldehyde/methylene glycol are not plausible at sites distant from the portal of entry.<br>(3) The idea that formaldehyde/methylene glycol transforms cells in the peripheral circulation or the nasal epithelium at the portal of entry, which can then migrate and incorporate into the bone marrow or other distant tissues to cause cancer, is not plausible. | [136] |
| F344 (n = 10 to 30 males/group) | 0.7, 2, 5.8, 9.1, 15.2 ppm; 6 hours | Measurable numbers of endogenous adducts were found in both the nasal mucosa and bone marrow, and exogenous adducts in the nasal mucosa. No exogenous adducts were detected in the bone marrow (on-column detection limit ~20 amol). | [61] |
| Cynomolgus macaques (n = 8 males) | 1.9, 6.1 ppm; 6 h/d, 2 days | Measurable numbers of endogenous and exogenous adducts were detected in the nasal tissues of both exposure groups, but only endogenous adducts in the bone marrow (on-column detection limit ~20 amol). | [63] |

## Table 9. Epidemiological studies of formaldehyde/methylene glycol and lymphohematopoietic cancers

| Study design; subjects or studies (n) | Exposure concentration or metrics | Results | Reference |
|---|---|---|---|
| **Cohort, case-control and molecular studies** | | | |
| Retrospective cohort mortality; Men employed after 1937 at six British factories where formaldehyde was produced or used, followed through 2000 (n = 14,014), compared with the general population | (a) Background: <0.1 ppm<br>(b) Low: 0.1 to 0.5 ppm<br>(c) Moderate: 0.6 to 2.0 ppm<br>(d) High: >2.0 ppm | There were 31 leukemia deaths in this cohort, which included 3,991 workers exposed to >2 ppm; 34 cases were expected. | [127,128] |
| Retrospective cohort mortality; Textile workers (82% female) employed after 1955 at 3 U.S. garment facilities, followed through 1998 (n = 11,039), compared with U.S. and local populations | (a) 8-h TWA (across all departments and plants) mean 0.15 ppm, range 0.09 to 0.2 ppm<br>(b) Age at first exposure: median 26.2, range 15.2–79.8 years<br>(c) Duration: <3, 3 to 9, ≥10 years<br>(d) Time since first exposure: <10, 10 to 19, ≥20 years<br>(e) Year first exposed: <1963, 1963 to 1970, ≥ 1971 | There were 59 leukemia cases in this cohort; 61 cases were expected. | [128,129] |
| Retrospective cohort | (a) Average intensity (8-h | This study reported and included 1,006 death certificates that a previous | [90,137] |

**Table 9. Epidemiological studies of formaldehyde/methylene glycol and lymphohematopoietic cancers**

| Study design; subjects or studies (n) | Exposure concentration or metrics | Results | Reference |
|---|---|---|---|
| mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants (NCI cohort; Plants #1-#10) and followed through 2004 (n = 25,619), compared with U.S. population | TWA): 0, 0.1 to 0.4, 0.5 to <1, ≥1.0 ppm<br>(b) Cumulative: 0, 0.1 to 1.4, 1.5 to 5.4, ≥5.5 ppm-years<br>(c) Ever vs. never exposed<br>(d) Peak: 0, 0.1 to 1.9, 2 to 4, ≥ 4.0 ppm<br>(e) Peak frequency: hourly, daily, weekly, monthly | paper missed for this cohort. There were proportionally greater numbers of missing deaths among the un-exposed and low-exposed groups used as internal referents in the previous paper.<br><br>There were 319 deaths from all LHP cancers (from a total of 13,951 deaths) in this cohort, including 286 "exposed" and 33 "non-exposed" cases. Based on U.S. mortality rates, neither of these groups showed statistically significant elevations in SMRs estimated for all LHP cancer, all leukemia, lymphatic leukemia, myeloid leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or multiple myeloma.<br><br>Statistically significant dose-response trends were reported for peak exposure and all LHP, all leukemia and Hodgkin's lymphoma deaths, as well as for average intensity of exposure and Hodgkin's lymphoma deaths. However, the relative risk (RR) for Hodgkin's lymphoma in workers with the highest average intensity was lower than for workers with lower average exposure.<br><br>No statistically significant trends were found among the LHP cancers and peak frequency or cumulative exposures. | |
| Nested case-control mortality; Deceased embalmers and funeral directors (n = 6,808) | (a) Average intensity while embalming: 0, >0 to 1.4, >1.4 to 1.9, >1.9 ppm<br>(b) Cumulative: 0, >0 to 4058, >4058 to 9253, >9253 ppm-hours<br>(c) Duration in jobs involving embalming: 0, >0 to 20, >20 to 34, >34 years<br>(d) Ever vs. never embalming<br>(e) Lifetime 8-hour TWA: 0, >0 to 0.1, >0.1 to 0.18, >0.18 ppm<br>(f) Number of embalmings: 0, >0 to 1422, >1422 to 9253, >9253<br>(g) Peak: 0, >0 to 7, >7 to 9.3, >9.3 ppm | There were 168 deaths attributable to LHP cancers in this cohort, including 99 lymphoid and 48 non-lymphoid cancers. Non-lymphoid cancers included 34 cases of myeloid leukemia. Statistically significant increases in risks of LHP cancers of non-lymphoid origin were found for several exposure metrics, including the highest levels of exposure for cumulative, TWA, and peak exposures, as well as for subjects who embalmed for >20 years.<br><br>For myeloid leukemia, strong, statistically significant associations with exposure duration, number of embalmings performed, and cumulative exposure were found. Statistically-significant dose-response relationships were reported between myeloid leukemia deaths and both exposure duration and peak exposure.<br><br>**Comment:** Several methodological issues have been identified for this study study. For example:<br>(1) Myeloid leukemia cases among the study subjects were 50% more likely than controls to have begun employment in the funeral industry before 1942; This suggests that they belonged primarily to an older and earlier population than the controls and likely explains why they performed more embalmings<br>(2) The single myeloid leukemia case in the control group yielded large, unstable confidence intervals; The odds ratios (ORs) were substantially reduced when the referent group included both the controls and the subjects performing <500 embalmings<br>(3) The myeloid leukemia cases and controls had nearly identical mean estimated average, 8-h TWA, and peak exposures; The cases had higher estimated number of embalmings and cumulative exposure than the controls, which can be explained by their earlier first employment, younger age at hire, and longer average employment in the industry, compared with controls. | 85,138-140 |
| Molecular epidemiology of formaldehyde workers and frequency-matched controls in China (n = 43; 51 controls) | Median ($10^{th}$-$90^{th}$ percentile):<br>(a) Formaldehyde workers: 1.28 (0.63-2.51) ppm<br>(b) Controls: 0.026 (0.0085-0.026) ppm | Statistically significant decreases were observed in mean red blood cell (RBC), white blood cell (WBC), granulocyte, and platelet counts in the subjects compared with the controls. Statistically significant increases were found in mean corpuscular volume (MCV) and in frequencies of chromosome 7 monosomy and chromosome 8 trisomy. No occupational co-exposures to benzene or other hemotoxic or genotoxic solvents were detected in this study. In a parallel experiment, statistically significant, dose-related decreases were observed in the number of colonies formed per plated cells from the subjects compared with controls.<br><br>**Comment:** Numerous problems in this preliminary study have been identified. For example:<br>(1) All of the blood counts in the exposed workers were within the reference range.<br>(2) The frequencies of the aneuploidies reported were seen only after 14 days of in vitro incubation, were high for cells from both the workers | 141-145 |

**Table 9. Epidemiological studies of formaldehyde/methylene glycol and lymphohematopoietic cancers**

| Study design; subjects or studies (n) | Exposure concentration or metrics | Results | Reference |
|---|---|---|---|
| | | and controls, and were not reported in either the factory workers or the controls in vivo.<br>(3) The most frequent chromosome aberrations associated with myeloid leukemia are translocations, but this study investigated neither translocations nor aneuploidies other than monosomy 7 and trisomy 8.<br>(4) Formaldehyde appears to be mutagenic predominantly by a clastogenic, not an aneugenic mode of action.<br>(5) Formaldehyde has been shown to damage several cell types directly exposed in vitro, an effect therefore not unique to myeloid progenitor cells. | |
| | | **Meta-analyses** | |
| Meta-analysis of cohort and case-control studies that reported leukemia rates in professional or industrial workers; (n = 18) | Not detailed | No statistically-significant associations were found between leukemia and exposure across all of the studies, across all cohort studies, or across all case-control studies. Slightly elevated risk of leukemia was reported among embalmers and pathologists/anatomists, but none for industrial workers, even those with the highest reported exposures. | [146] |
| Meta-analysis of cohort studies of professional or industrial workers through February 2007 (n = 25) | Not detailed | A "modestly elevated" pooled RR for LHP cancers was calculated for professionals (ie, embalmers, anatomists and pathologists; 8 studies), but not for industrial workers (4 studies). Similar results were reported for leukemia. | [128] |
| Meta-analysis of cohort and case-control studies that reported LHP cancer rates in professional or industrial workers (n = 26) | Not detailed | Summary RRs for professional and industrial workers combined were increased for all LHP cancers combined (19 studies). Statistically significant increases in RRs were reported for all leukemias (15 studies) and myeloid leukemia (6 studies).<br><br>**Comment:** These authors attempted to increase the statistical power of their analysis by focusing only on the highest exposure groups in each study, selecting exposure duration from some studies, and peak, average, or cumulative exposure from others. They preferentially selected results for myeloid leukemia, rather than results for all types of leukemia combined, when available. They did not stratify the data to distinguish low-exposure professionals from high-exposure industry workers. | [147] |
| Meta-analysis of case-control and cohort studies that reported myeloid leukemia rates in professional or industrial workers (n = 14) | Not detailed | Statistically significant increases in summary RRs for professional and industrial workers combined were observed for leukemia and myeloid leukemia. Statistically significant increases in summary RRs were calculated for industrial workers (6 studies) and professionals (8 studies) considered separately.<br><br>**Comment:** These authors attempted to increase the statistical power of their analysis by focusing only on the highest exposure groups in each study, selecting exposure duration from some studies, and peak, average, or cumulative exposure from others. They preferentially selected results for myeloid leukemia, rather than results for all types of leukemia combined, when available. | [148] |
| Meta-analysis of cohort and case-control studies of professional and industrial workers through May 2009 (n = 17) | Not detailed | For leukemia, no statistically significant increases in summary RRs were found in the cohort or the case-control studies for professionals (ie, embalmers and technical workers) and industrial workers combined. No statistically significant increases was observed in the summary RRs calculated specifically for professional workers (15 studies), for industrial workers (2 studies), or for myeloid leukemia from the cohort studies. Although the authors found that their summary proportionate mortality ratio (PMR) for leukemia was elevated (PMR = 1.44; 95% CI: 1.25- 1.67; 3 studies), they explained that PMRs are unreliable and sugested that the inclusion of PMR studies may have caused inaccurately elevated summary risk estimates in previous meta-analyses. | [149] |

**Table 10. Reproductive and developmental toxicity studies of formaldehyde/methylene glycol in test animals**

| Species (n) | Concentration(s); volume; duration | Results | Reference |
|---|---|---|---|
| | | **Multiple dose studies** | |
| Wistar rats (n = 6 males/group) | 0, 5, 10 ppm; 8 h/d, 5 d/wk, 91 days | Exposure to 5 or 10 ppm caused unsteady breathing, excessive licking, frequent sneezing, and hemorrhage of nasal mucosa. Statistically significant decreases in serum testosterone concentrations and seminiferous tubule diameters were found in both groups of exposed rats compared with controls. Hsp70 levels were increased in the spermatogonia, spermatocytes, and spermatids of the treated rats compared with controls. | [46] |
| Sprague-Dawley rats (n = 10 males/group) | 8 ppm; 12 h/d, 2 weeks | Significant decrease in testicular weight was found in the exposed rats compared with the controls. Histopathological examination revealed seminiferous tubule atrophy, interstitial vascular dilatation and hyperemia, disintegration and shedding of seminiferous epithelial cells into azoospermic lumina, and interstitial edema in the testes of the exposed rats. Statistically significant decreases were reported in epididymal sperm count, percentage of motile sperm, activities of testicular superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and in glutathione (GSH) levels, and increase in malondialdehyde (MDA) levels in the exposed rats compared with controls. All of these effects were markedly decreased in exposed rats that were also treated with Vitamin E. These authors did not report the overt toxic effects of the exposures. | [150] |
| Wistar rats (n = 7 males/group) | 1.5 ppm; 4 h/d, 4 d/wk; 2 h/d, 4 d/wk; or 4 h/d, 2 d/wk; 18 weeks | Statistically significant decreases in diameter and height of seminiferous tubules/testis were observed in the exposed rats compared with controls. Severe decreases were found in the number of germ cells in the seminiferous tubules and evidence of arrested spermatogenesis after exposure 4 h/d, 4 d/wk, decrease in the number of germ cells and increased thickness of the tubule basement membrane after exposure 2 h/d, 4 d/wk, and disruption in the arrangement of Sertoli and germinal cells, with increased spacing between germ cells, after exposure 4 h/d, 2 d/wk. The authors did not report the overt toxic effects of the formaldehyde exposures. | [151] |
| Mice, strain not specified (n = 12 males/group) | 0, 16.9, 33.8, 67.6 ppm; 2 h/d, 6 d/wk, 13 weeks | A statistically significant increase in the sperm aberration rate and decrease in mean live fetuses/litter in a dominant-lethal test were observed after exposure to 67.6 ppm. Resorption rates were statistically significantly increased for all groups of exposed rats. The English abstract of this Chinese paper does not detail the exposure method or report the overt toxic effects of the exposures. | [152] |
| Wistar rats (n = 10 males/group) | 0, 6, 12 ppm; 6 h/d, 5 d/wk, 30 days | Lower numbers of both granular cells in the hippocampal dentate gyrus and pyramidal cells in the cornu ammonis of the hippocampus were observed at post-natal day 90 (PND90), compared to PND30, in rats exposed to 12 ppm. The authors did not report the overt toxic effects of the formaldehyde exposures. | [47,153] |
| Sprague-Dawley rats (n = 6 dams/group) | 0, 6 ppm; 8 h/d, 6 weeks, starting on gestation day 1 (GD1), post-natal day 1 (PND1), or at 4 weeks of age or adulthood | Statistically significant decreased mean body and liver weights were observed in the offspring when exposure began on GD1. Liver weights were statistically significantly increased when exposure began at 4 weeks of age compared with controls. In the liver, statistically significant increases in catalase (CAT) activity and malondialdehyde (MDA) concentration, and decreases in glutathione (GSH) concentration and superoxide dismutase (SOD) activity were observed in the offspring when exposure began on GD1, PND1, or at 4 weeks of age. The authors did not report the overt toxic effects of the formaldehyde exposures. | [154] |

**Table 11. Epidemiological studies of formaldehyde/methylene glycol and reproductive effects**

| Study design; subjects or studies (n) | Exposure concentration or metrics | Results | Reference |
|---|---|---|---|
| Case control; Women who worked full-time in cosmetology and had a spontaneous abortion or a live baby during 1983−1988 (n = 376; 61 with spontaneous abortions, 315 with live births) | Exposed vs. unexposed | An association was reported between spontaneous abortion and use of "formaldehyde-based" disinfectants (crude odds ratio = 2.0; 95% CI: 1.1-3.8). The association was still apparent (adjusted odds ratio = 2.1; 95% CI: 1.0−4.3) after adjusting for maternal characteristics (eg, age, smoking, glove use, other jobs) and other workplace exposures (eg, chemicals used on hair, use of manicure products). | 49 |
| Case-control; Women occupationally exposed to formalin in hospital laboratories and having a spontaneous abortion, compared to controls who delivered a baby without malformations, during 1973−1986 (n = 208; 329 controls) | Mean: 0.45 ppm (range: 0.01-7 ppm) reported in similar laboratories | A statistically significant association was found between exposure to formalin/formaldehyde 3 to 5 d/wk and incidence of spontaneous abortions, after adjusting for employment, smoking, alcohol consumption, parity, previous miscarriage, birth control failure, febrile disease during pregnancy, and exposure to other organic solvents in the workplace. Exposures to toluene and xylene were also statistically significantly associated with the incidence of spontaneous abortions. No association was found between formalin exposure and congenital malformations in laboratory workers (n = 36) compared with controls (n = 5). | 50 |
| Case-control; Women occupationally exposed in woodworking industries, compared with employed, unexposed women (n = 602; 367 controls) | TWAs:<br>(a) Low: 0.1 to 3.9 ppm<br>(b) Medium: 4.0 to 12.9 ppm<br>(c) High: 13.0 to 63 ppm | Statistically significant decrease was observed in fecundability density ratios (FDRs; ie, the average pregnancy incidence density of the exposed women divided by that of the unexposed women) for the high exposure group, and in the women in the high exposed group who did not wear gloves (n = 17). The reduced FDR among women in the high exposed group who wore gloves was not statistically significant (n=22). Associations were found between exposure and spontaneous abortions in 52 women who had worked in their workplace during the year of the spontaneous abortion and at the beginning of the time-to-pregnancy period. The odds ratios (ORs) were 3.2 (95% CI: 1.2−8.3), 1.8 (95% CI: 0.8−4.0), and 2.4 (95% CI: 1.2−4.8) for the low, medium, and high exposure categories, respectively. Endometriosis also appeared to be associated with exposure in women in the high exposure category (OR = 4.5; 95% CI: 1.0−20.0). | 51 |
| | | **Meta-analysis** | |
| Meta-analysis of cohort, case-control and cross-sectional studies of professional or industrial workers through September 1999 (n = 8) | Up to 3.5 ppm | An overall meta-relative risk (meta-RR) estimate of 1.4 (95% CI: 0.9-2.1) was calculated, suggesting an association between occupational exposure and spontaneous abortion. However, no increased risk was observed after adjusting this estimate for reporting and publication biases (meta-RR = 0.7; 95% CI: 0.5-1.0). | 155 |

**Table 12. Measured formaldehyde levels during use of hair smoothing products**

| Test | Form Levels (ppm) | Exposure Time (min) | Samples ≥ Guidelines | | |
|---|---|---|---|---|---|
| | | | US NAC AEGL-1[a] 0.9ppm ≥ 10 min | ACGIH TLV®-Ceiling[b] 0.3 ppm | WHO 30 min Guideline[c] 0.08 ppm |
| **Oregon OSHA** | 0.074-1.88 | 6-48 | Yes (4) | Yes (9) | Yes (All ≥30 min) |
| **Exponent 1** | 0.170-0.269 | 95-141 | No | No | Yes (All) |
| **Exponent 2** | 0.041-0.76 | 17-43 | No | Yes (9) | Yes (6 ≥30 min) |
| **Tennessee OSHA** | 0.3-1.07 | 15 | Yes (1) | Yes (5) | Yes[d] |
| **PKSC 1** | 0.761-1.71 | 15 | Yes | Yes (All) | Yes[e] |
| **PKSC 2** | 0.189-0.395 | 86-117 | No | Yes | Yes[f] |

[a]National Advisory Committee Interim Acute Exposure Guideline Level-1 (concentration above which the general population could experience notable discomfort, irritation, or other effects)
[b]American Conference of Government Industrial Hygienists Threshold Limit Value Ceiling (concentration that should not be exceeded during any part of the working day)
[c]World Health Organization Guideline for Indoor Air Quality
[d]calculated levels exceed by up to 4 fold
[e]calculated levels exceed by 12-21 fold
[f]calculated levels exceed by up to 5 fold

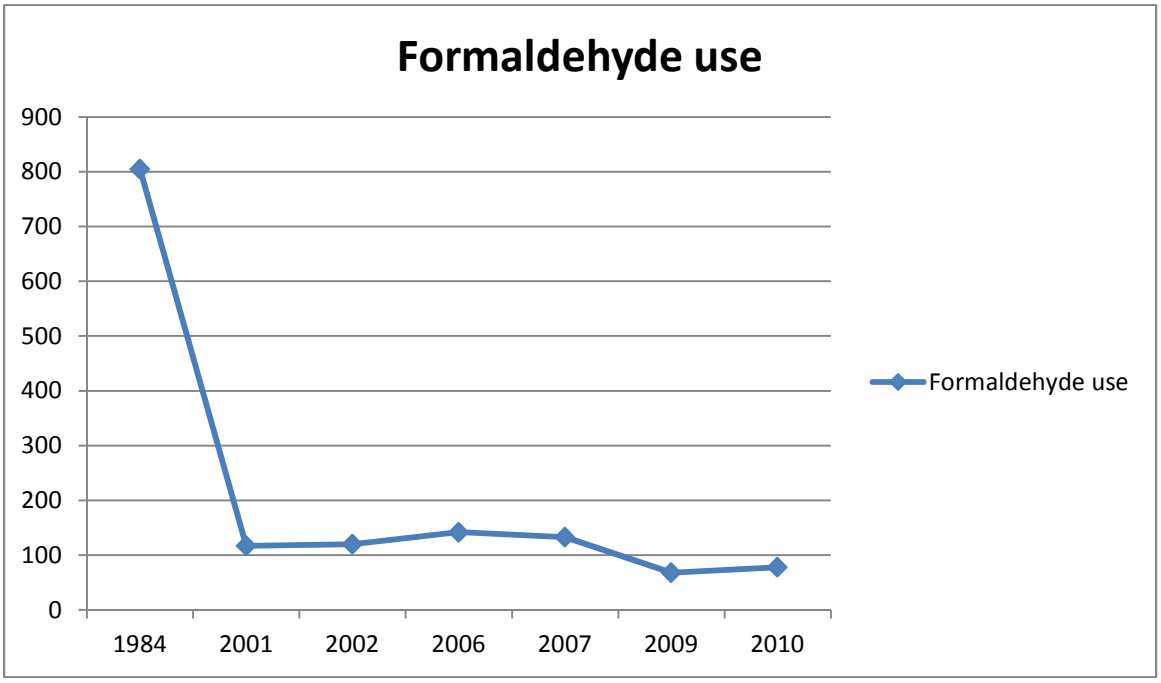



**Figure 1. Declining use of formaldehyde in cosmetic products as reported to the FDA VCRP (The x-axis is not linear).**

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