Persuasive Evidence that Formocresol Use in Pediatric Dentistry Is Safe

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ABSTRACT

Concern has been expressed about the safety of formocresol use in pediatric dentistry. Formaldehyde, a primary component in formocresol, is a hazardous substance and is considered a probable human carcinogen by Health Canada. However, humans inhale and ingest formaldehyde daily and also produce this compound as part of normal cellular metabolism. The human body is physiologically equipped to handle this exposure through multiple pathways for oxidation of formaldehyde to formate and incorporation into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways. Recent re-evaluation of earlier research that examined potential health risks associated with formaldehyde exposure has shown that the research was based on flawed assumptions, which resulted in erroneous conclusions. This review examines more recent research about formaldehyde metabolism, pharmacokinetics and carcinogenicity, the results of which indicate that formaldehyde is probably not a potent human carcinogen under conditions of low exposure. Extrapolation of these research results to pediatric dentistry suggests an inconsequential risk of carcinogenesis associated with formaldehyde use in pediatric pulp therapy. Areas for further investigation are suggested.

MeSH Key Words: carcinogens/toxicity; formaldehyde/chemistry; formocresols/toxicity; pulpotomy/methods

The suggestion that formocresol use in pediatric dentistry is unwarranted because of safety concerns has been promoted (unsuccessfully in North America) for several decades. This has stimulated investigations of alternatives to formocresol pulpotomy, some of which have shown efficacy equivalent to that of the latter procedure. Such research into alternatives is not only welcome but also absolutely necessary, as there can be no doubt that a reparative, biological approach to pediatric pulp therapy is preferable to the absolutist, devitalization approach of formocresol pulpotomy or primary tooth pulpectomy. However, until that goal is achieved, formocresol should continue to be used in pediatric pulp therapy. This commentary will demonstrate, through a thorough review of the relevant literature, that formocresol is indeed safe for children and that the “evidence” for banning this medicament has been either misinterpreted or replaced by better science.

Formaldehyde Is Ubiquitous

Formaldehyde is found in the air we breathe, the water we drink and the food we eat. Although daily intake from food is difficult to evaluate, the World Health Organization has estimated it at 1.5 to 14 mg/day (mean 7.8 mg/day); Owen and others estimated daily formaldehyde intake from food in a North American diet at 11 mg/day. Engine exhaust from cars and trucks without catalytic converters contains formaldehyde, and the
compound is also found in or released from many house-
hold products such as antiseptics, dishwashing liquids, 
fabric softeners, carpet cleaners, nail polish, nail hardener 
and some dermatologic products, paper products, adhe-
sives, latex paints, plastics, some permanent press fabrics, 
various wood products and tobacco products. In unpopu-
lated areas, outdoor air contains approximately 0.2 parts 
per billion (ppb) formaldehyde, but in populated areas, 
with truck and automobile traffic, air concentrations 
range between 10 and 20 ppb. In 2002–2003 Health 
Canada4 found levels of formaldehyde of 2 to 81 ppb in the 
air inside several homes in Prince Edward Island and in 
Ottawa. The National Institute for Occupational Safety 
and Health5 in the United States has stated that formalde-
hyde is immediately dangerous to health and life at con-
centrations of 20 parts per million (ppm) and higher. 
Second-hand cigarette smoke may contain up to 0.4 ppm 
of formaldehyde.6

Daily formaldehyde exposure is, therefore, a fact of 
life. Assuming a contribution of 9.4 mg/day from food, 
1 mg/day from inhalation and 0.15 mg/day from water, an 
adult takes in 10.55 mg of formaldehyde per day.1 Children 
are exposed to a lesser amount because of lower food 
intake, but at present there are no estimates of pediatric 
exposure. The estimated dose of formaldehyde associated 
with one pulpotomy procedure, assuming a 1:5 dilution of 
formocresol placed on a number 4 cotton pellet that has 
been squeezed dry, is 0.02 to 0.1 mg (author’s calculation).

Given the environmental ubiquitousness of formalde-
hyde and the recognized daily intake by humans, it is 
highly unlikely that the elimination of the microgram 
quantities of formaldehyde associated with formocresol 
pulpotomy will have a significant impact on a child’s daily 
exposure.

Pharmacokinetics of Formaldehyde

In addition to their inhalation and ingestion of 
formaldehyde, humans produce formaldehyde as part of 
normal cellular metabolism. For example, formaldehyde is 
formed during amino acid metabolism, oxidative 
demethylation, and purine and pyrimidine metabolism.7 
Moreover, humans are well equipped physiologically to 
handle this exposure through multiple pathways for 
conversion of formaldehyde and its oxidation product 
formate. The single carbon atom released during the 
metabolism of formaldehyde and formate is deposited in the “one carbon pool” which, in turn, is used for the 
biosynthesis of purines, thymidine, and other amino acids 
that are incorporated into RNA, DNA and proteins 
during macromolecular synthesis. Endogenous levels of 
metabolically produced formaldehyde range from approx-
imately 3 to 12 ng/g tissue.8

Extensive study of the metabolic pathways of 
formaldehyde has demonstrated that cystolic alcohol 
(dehydrogenase, mitochondrial aldehyde dehydrogenase 
and glutathione-dependent and glutathione-independent 
dehydrogenases are important enzymes in the metabolism 
of formaldehyde in hepatocytes,9 oral mucosa10 and nasal 
respiratory mucosa.11 The principal oxidative product of 
formaldehyde is formate, which is further oxidized to 
carbon dioxide and water by the action of formyltetrahy-
drofolate synthetase.12 In alternative pathways, formate 
may be converted to a soluble sodium salt and excreted in 
the urine, or it may be incorporated into the one-carbon 
pool for use in biosynthesis.13,14

Exogenous formaldehyde is taken up into the human 
body via ingestion, inhalation and dermal exposure. 
Ingested formaldehyde is readily absorbed by the gastroin-
testinal tract, and exhibits little subacute toxicity after oral 
exposure.15 Inhaled formaldehyde appears to be readily 
absorbed by the upper respiratory tract but is not distrib-
uted throughout the body because it is so rapidly metabo-
lized.16 Experiments in rats, monkeys and humans have 
shown no significant differences in formaldehyde concen-
tration in the blood before and immediately after exposure 
by inhalation. Using gas chromatography and mass spec-
trometry to measure blood formaldehyde concentrations 
in Fischer 344 rats exposed to a very high formaldehyde 
concentration (14.4 ppm for 2 hours) and in unexposed 
controls, Heck and others16 showed that the blood concen-
trations of the 2 groups were virtually identical. 
Casanova and others17 reported that the concentration of 
formaldehyde in the blood of rhesus monkeys following 
prolonged exposure to a high concentration of inhaled 
formaldehyde (6 ppm for 6 hours/day, 5 days per week for 
4 weeks) had no significant effect on the concentration of 
formaldehyde in blood relative to pre-exposure levels. 
Blood concentrations of formaldehyde were measured in 
6 human volunteers exposed for 40 minutes to 1.9 ppm 
formaldehyde16 (a concentration that is considered slightly 
irritating to the nasal and conjunctival membranes), but 
the concentrations before exposure were not significantly 
different from those measured immediately after expo-
sure. The average concentration of formaldehyde in the 
blood of rats, monkeys and humans was 2.70 ± 0.15 µg/g 
(mean ± standard error), or approximately 0.1 mmol/L. 
In dermal studies, formaldehyde was absorbed less readily 
by monkeys than by rats or guinea pigs.18

Following intravenous infusion, the biological half-
life of formaldehyde in monkey blood is about 1.5 minutes, 
with a concurrent rise in formic acid levels19 indicating 
metabolism of the formaldehyde. In rats, metabolism of 
formaldehyde after administration via the pulp chamber is 
also rapid, and the majority of conversion reportedly 
occurs within 2 hours after administration.20 Exogenous 
formaldehyde is cleared from human plasma with a bio-
logical half-life of 1 to 1.5 minutes.21 In dogs, the conver-
sion of formate to carbon dioxide and water results in a 
biological half-life for formate of about 80 to 90 minutes.12
In humans, the liver converts formaldehyde to carbon dioxide at a rate of 22 mg/min.\textsuperscript{3,22,23} In mice and rats, the metabolites of formaldehyde are eliminated in urine, feces and expired air, the relative proportion depending on the route of administration.\textsuperscript{24,25} Higher urine concentrations of formic acid were found in 3 of 6 workers occupationally exposed to unspecified concentrations of formaldehyde in air (30.0, 50.5 and 173.0 mg/L, respectively) than in unexposed workers (17 mg/L).\textsuperscript{26}

Formaldehyde also reacts covalently with amino and sulfhydryl groups in target tissues and with DNA, forming unstable hydroxymethyl protein adducts (DNA–protein cross-links [DPX]) and, in a second slower reaction involving recruitment of a second amino group, methylene cross-links.\textsuperscript{27,28} However, in rat and monkey tissues, metabolism of formaldehyde and its elimination by pathways other than DPX formation overwhelmingly predominate.\textsuperscript{29}

Results from dental pulp studies involving rats, dogs and monkeys showed that formaldehyde labelled with radioactive carbon (\textsuperscript{14}C) was distributed among the muscle, liver, kidney, heart, spleen and lungs, although the quantities detected were very small (1% of the total administered dose).\textsuperscript{20,30–32} Myers and others\textsuperscript{31} and Pashley and others\textsuperscript{32} concluded that [\textsuperscript{14}C]formaldehyde is absorbed systemically from pulpotomy sites. However, their studies were poorly controlled and did not determine whether the labelling of tissues occurred by metabolic incorporation of the [\textsuperscript{14}C] moiety of the labelled formaldehyde into macromolecules or by covalent binding (formation of protein adducts). In an unrelated study, Casanova-Schmitz and others\textsuperscript{33} sampled the venous blood of rats after injecting either [\textsuperscript{14}C]formaldehyde or [\textsuperscript{14}C]formate into the tail vein. They verified that labelling of proteins and target tissues was due to metabolic incorporation of the radiolabelled metabolite of formaldehyde and not covalent binding. The profiles of radioactivity in the blood after these injections were similar regardless of whether [\textsuperscript{14}C]formaldehyde or [\textsuperscript{14}C]formate was the source of [\textsuperscript{14}C]. These results excluded the possibility that the labelling of blood macromolecules was due to formation of protein adducts by formaldehyde, since only [\textsuperscript{14}C]formaldehyde is capable of forming protein adducts, whereas both [\textsuperscript{14}C]formaldehyde and [\textsuperscript{14}C]formate are precursors for macromolecular synthesis by the one-carbon pool.

**Mutagenicity, Genotoxicity and Cytotoxicity**

Exposure of cells to formaldehyde leads to the formation of DPX.\textsuperscript{34} The most common types of DNA damage induced by formaldehyde are clastogenic lesions, including sister chromatid exchanges (SCE), micronuclei and chromosomal aberrations.\textsuperscript{35} and deletions.\textsuperscript{36} Levels of formaldehyde-induced DPX are considered to represent a good molecular dosimeter of formaldehyde exposure at sites of contact and are frequently used for risk modelling and prediction of formaldehyde carcinogenicity for different species.\textsuperscript{37–39} DPX have been shown to occur only at the site of initial contact in the nasal mucosa of rats and in the upper respiratory tract of monkeys exposed to formaldehyde.\textsuperscript{38,39}

It has also been proposed that formaldehyde could induce the development of DPX at distant sites but no convincing evidence has been obtained from in vivo experimental studies. The outcomes of these studies have included (1) lack of detectable protein adducts or DPX in the bone marrow of normal rats exposed to formaldehyde labelled with radioactive hydrogen (\textsuperscript{3H}) or carbon (\textsuperscript{14}C) at concentrations as high as 15 ppm,\textsuperscript{33} (2) lack of detectable protein adducts or DPX in the bone marrow of glutathione-depleted (metabolically inhibited) rats exposed to [\textsuperscript{3H}]formaldehyde and [\textsuperscript{14}C]formaldehyde at concentrations as high as 10 ppm,\textsuperscript{32,40} (3) lack of detectable DPX in the bone marrow of rhesus monkeys exposed to [\textsuperscript{14}C]formaldehyde at concentrations as high as 6 ppm,\textsuperscript{49} and (4) failure of formaldehyde to induce chromosomal aberrations in the bone marrow of rats exposed to airborne concentrations as high as 15 ppm\textsuperscript{44} or of mice receiving intraperitoneal injections of formaldehyde at doses as high as 25 mg/kg.\textsuperscript{41}

In a recent issue of this journal, Casas and others\textsuperscript{42} cited 2 studies as evidence of the genotoxic and mutagenic effects of formaldehyde.\textsuperscript{43,44} However, those published articles in fact represent the same study, the first article reporting interim results of nasal tumour development in rodents\textsuperscript{43} and the second (3 years later)\textsuperscript{44} reporting the final results for the same study. Although Kerns and others\textsuperscript{44} discussed the mutagenic potential of formaldehyde in their animal model, they did not in fact report results pertaining to mutagenicity, as was stated by Casas and others.\textsuperscript{42} More recent research by Heck and Casanova\textsuperscript{45} has revealed that the development of DPX in nasal tissues of rat and upper respiratory tract of primates are associated only with exposure to high doses of formaldehyde; at ambient concentrations consistent with environmental exposures, DPX are unlikely to occur. Furthermore, Quijvryn and Zhitkovich\textsuperscript{46} have shown that DPX do not persist in tissues for more than a few hours and undergo either spontaneous hydrolysis or active repair by proteolytic degradation of cross-linked proteins, thereby calling into question the role of DPX in formaldehyde-induced carcinogenesis.

Cytogenetic studies\textsuperscript{47} of lymphocytes from rodents following formaldehyde inhalation with exposures ranging from 0.5 to 15 ppm for 6 hours per day for 5 days failed to detect either chromosomal aberrations or sister chromatid exchanges at any of the formaldehyde concentrations. The authors attributed their negative results to the pharmacokinetics of formaldehyde.

In vitro experiments with a Chinese hamster cell line\textsuperscript{46} found that DPX and SCE as a result of formaldehyde
exposure were associated with cytotoxicity, not mutation. However, no mutagenesis occurred in cultured human lymphocytes below a formaldehyde threshold of 5 µg/mL in the culture medium. Dental studies have not supported the contention that formaldehyde, as used in dentistry, is mutagenic. Zarzar and others performed formocresol pulpotomy on 20 children using Buckley’s original formula (19% formaldehyde and 35% cresol in a solution of 15% glycerin and water). Peripheral venous samples were collected from each child immediately before and 24 hours after the pulpotomy, and lymphocytes were collected from each blood sample for cell culture and cytogenetic analysis. No statistically significant differences were found between the 2 groups in terms of chromosomal aberrations, chromatid breaks or chromatid gaps, and Zarzar and others concluded that formocresol is not mutagenic. The authors did observe chromosomal aberrations in 1 (5%) of the 20 patients but were unable to determine whether formocresol or other variables accounted for this finding.

Ribeiro and others reported 2 studies that assessed the mutagenic potential of formocresol as well as several other chemicals commonly used in dentistry. Using a mouse lymphoma cell line and cultured human fibroblasts and a series of dilutions of formocresol similar to clinical doses, these authors found that formocresol did not produce detectable DNA damage and should not be considered genotoxic.

Laboratory investigations of root canal sealers containing formaldehyde, which are used in endodontic procedures, have demonstrated cytotoxicity. However, for several reasons, these investigations are not comparable to formocresol pulp studies. A larger quantity of formaldehyde is released from root canal sealers than during pediatric formocresol pulpotomy because of the large quantity of sealer used. Moreover, contact of formocresol with vital pulp tissue during pulpotomy is restricted to only a few minutes, whereas root canal sealer remains in the root canal and forms part of the final restoration, with the potential for further release of formaldehyde.

In summary, the development of DPX has been demonstrated only after prolonged exposure to formaldehyde at specific contact sites such as the nasopharynx. Hence, the argument that the microgram quantities of formaldehyde applied to pediatric pulp tissue for a few minutes will induce distant-site genotoxicity is not supported by the available evidence.

Carcinogenicity

That cancer develops in experimental animals after inhalation of air with high concentrations of formaldehyde is indubitable. These cancers occur as a result of long-term, direct contact between the formaldehyde and susceptible tissues. The resultant toxic effects at these initial contact sites include ulceration, hyperplasia and squamous metaplasia and “are considered to contribute to the subsequent development of cancer.” However, these high-dose responses are unlikely to occur at sites distant from the point of initial formaldehyde contact (such as the bone marrow) because, according to a large body of undisputed evidence, formaldehyde is not delivered to these distant sites. Those who have argued against the continued use of formocresol in pediatric dentistry on the basis that “formaldehyde causes cancer” have failed to recognize this very important distinction.

Casas and others cited the work of Swenberg and others and Kerns and others to support their argument about carcinogenicity. In fact, the 2 studies led by Swenberg and Kerns are the same study, with Swenberg and others reporting interim results after 18 months and Kerns and others reporting final results after 30 months. This group of researchers showed that nasal squamous cell carcinoma developed in Fischer 344 rats exposed to formaldehyde gas at concentrations of 6 ppm and higher for 6 hours/day, 5 days per week for 24 months. However, the formaldehyde concentrations that resulted in cancer were more than 1,000 times typical human environmental exposures and 8 times the U.S. occupational exposure limit (0.75 ppm) and are therefore not representative of human experience. Moreover, the experimental conditions that resulted in nasal cancers in rodents in no way resemble the conditions associated with a 5-minute exposure to microgram quantities of formaldehyde, as experienced by a child undergoing formocresol pulpotomy.

Until recently, formaldehyde was classified as a “probable human carcinogen” by Health Canada, the International Agency for Research on Cancer (IARC), the Agency for Toxic Substances and Disease Registry (ATSDR) in the U.S. Department of Health and Human Services, and the U.S. Environmental Protection Agency (USEPA). Although they lacked sufficient evidence to demonstrate the development of cancer in exposed humans, these regulators (Health Canada, ATSDR and USEPA) and advisory agency (IARC) predicted the cancer risk posed by low-dose exposure by extrapolating from the laboratory animal data cited previously.

However, various researchers have recognized that significant anatomic and physiologic differences between humans and other animal models confounded extrapolation of animal data to humans. Researchers at the Chemical Industry Institute for Toxicology Centers for Health Research (CIIT) developed dynamic 3-dimensional airflow models that accurately depicted both airflow and regional deposition of formaldehyde on mucosal surfaces of rodents, monkeys and humans. The improved understanding garnered from this research allowed the researchers to improve the accuracy of computer-generated predictions of the uptake and absorption of formaldehyde in each animal model. The CIIT researchers also developed a biologically motivated...
considered a “low exposure condition.” The USEPA Office of Economic Cooperation and Development has stated, on the basis of the CIIT research models, that “taking into account the extensive information on its mode of action, formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions.”66 Pediatric pulp therapy using formocresol as recommended would be considered a “low exposure condition.” The USEPA Office of Air Quality Planning and Standards has stated, “The dose response value in the EPA Integrated Risk Information System (IRIS) [for formaldehyde] is based on a 1987 study and no longer represents the best available science in the peer reviewed literature. We believe that the CIIT modeling effort represents the best available application of mechanistic and dosimetric science on the dose-response for portal of entry cancers due to formaldehyde exposure.”67

The possibility that inhaled or ingested formaldehyde may induce cancers at sites distant from the respiratory or gastrointestinal tracts has been investigated in numerous long-term toxicity studies performed in rodents.54 Leukemia was not observed in any of 7 long-term inhalation bioassays in rodents nor was it observed in 3 drinking water studies in which rodents were exposed to doses as high as 1.9 to 5 g/L. Leukemia was observed in a single drinking water study66 in which Wistar rats were exposed to doses as high as 1.5g/L, but that study is regarded by the Cancer Assessment Committee of the Food and Drug Administration in the United States59 as questionable and the data unreliable because of a lack of critical detail and questionable histopathological conclusions.

Evidence from epidemiology investigations of industrial workers with exposure to formaldehyde provide weak and inconsistent evidence that such exposure is associated with leukemia. Importantly, the researchers in each instance failed to use recognized epidemiologic criteria to evaluate the hypothesis that formaldehyde exposure leads to cancer. The results of 2 large American studies, one from the NCI37 and the other from the National Institute of Occupational Safety and Health,70 did not support a strong causal relation between formaldehyde exposure and leukemia, and the strength of association — the extent to which a collective body of data indicates a positive association between a disease, in this case leukemia, and a suspected causative agent, in this case formaldehyde — was weak (standardized mortality ratio of 0.86). Moreover, a study of British chemical workers, sponsored by the Medical Research Council Environmental Epidemiology Unit in the United Kingdom71 and involving the highest chronic formaldehyde exposures and highest peak exposures of all 3 investigations, showed no causal relationship between formaldehyde and leukemia.

Therefore, evidence from both experimental investigations and epidemiologic research do not support the hypothesis that inhaled or ingested formaldehyde may induce distant-site toxicity. The abundant negative evidence mentioned previously is undisputed and strongly suggests that there is no delivery of inhaled, ingested or topically applied formaldehyde to distant sites. Combined with the facts that formaldehyde occurs naturally throughout the body, that there are multiple pathways for detoxification and that only microgram quantities of formaldehyde are applied to pulp tissues during pulpotomy procedures for mere minutes, the negative findings
provide convincing evidence that exposure of children to the formaldehyde component of formocresol during a pulpotomy is insignificant and inconsequential.

**Immune Sensitization**

Despite evidence from dogs that formocresol can produce antigenic activity in dental pulp tissue, Rolling and Thulin found no increase in either immune response or allergic reactions in 128 children who had undergone formocresol pulpotomy.

More recent evidence supports the work of Rolling and Thulin. A Canadian study of urea formaldehyde foam insulation (UFFI) off products in the homes of subjects with asthma found that long-term exposure had no effect on immunologic parameters. Doi and others found that the prevalence of IgE sensitization to formaldehyde was very low among Japanese children, regardless of whether they had asthma; furthermore, they found no clinical relevance of formaldehyde-specific IgE. Hence, the suggestion that formocresol “sensitizes” children has not been supported.

**Where Do We Go from Here?**

On the basis of the evidence presented in this review, it is highly unlikely that formocresol, judiciously used, is genotoxic or immunotoxic or poses a cancer risk to children who undergo one or more formocresol pulpotomy procedures. However, definitive data to support this hypothesis are lacking, and such evidence is needed before definitive conclusions can be reached.

In keeping with accepted therapeutic principles, pediatric dentists who wish to continue to use formocresol should apply the lowest dose possible for the shortest time possible to obtain the desired effect. To that end, a 1-in-5 dilution of Buckley’s formocresol is recommended. The dilution should be performed in the local pharmacy to ensure accuracy. Recent research has indicated that a minority of pediatric dentists use dilute formocresol because it is not available commercially, so perhaps it is time for the manufacturers of formocresol products to develop and market a 1-in-5 dilution of this medicament to replace the “full-strength” formulations now available, especially given that the effects of the 2 formulations are equivalent.

The author has calculated that a number 4 cotton pellet soaked in full-strength formocresol and then squeezed dry could theoretically deliver a dose of 0.1 to 0.5 mg formocresol to the dental pulp. A number 4 pellet soaked in a 1-in-5 dilution of formocresol, squeezed dry and applied for 5 minutes or less could deliver 0.02 to 0.1 mg. However, the actual dose delivered to the pulp tissue is probably much smaller in both cases, as most of the formocresol will remain in the cotton pellet. Determining the actual dose delivered represents an important area for further investigation. In addition, efforts are needed to disseminate information about dose delivered.

It is important to put this discussion into a broader perspective. Antibiotics are used in dentistry at least as often as formocresol, and each year numerous children and adults are injured or die as a result of allergic or anaphylactic reactions to antibiotics, yet there has been no call for the elimination of antibiotics from dental practice. In fact, there is an acceptance that an allergic reaction is both a possibility and a risk in the treatment of dental infection. Peroxides for dental bleaching, bonding agents and solvents used in adhesive dentistry and mercury released from amalgam are other examples of potentially dangerous chemicals that are used in pediatric dentistry without warnings to parents and patients of the associated risks. Singling out one chemical such as formocresol for elimination from practice protocols in the face of a complete lack of human experimental data identifying a clear risk is intellectual tomfoolery.

On the basis of the evidence presented in this review, the risk of cancer, mutagenesis or immune sensitization associated with the proper use of formocresol in pediatric pulp therapy can be considered inconsequential. Until a superior alternative is developed or there is definitive evidence substantiating a cancer risk, there is no reason to discontinue its use. When used judiciously, formocresol is a safe medicament.

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