

Conference Paper

Is Formocresol Obsolete? A Fresh Look at the Evidence Concerning Safety Issues

Alan R. Milnes, DDS, PhD

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 the International Agency for Research on Cancer, Health Canada, the Agency for Toxic Substances and Disease Registry in the U.S. Department of Health and Human Services, and the U.S. Environmental Protection Agency. Humans inhale and ingest formaldehyde daily, however, and produce formaldehyde during cellular metabolism. The human body is physiologically equipped to handle formaldehyde through multiple conversion pathways. The resultant single carbon atom released during metabolism is deposited in the "1-carbon pool," which, in turn, is used for the biosynthesis of macromolecules including DNA and RNA. Reevaluation of earlier research that examined potential health risks associated with formaldehyde exposure has shown that this research was based on flawed assumptions, which resulted in erroneous conclusions. The purpose of this review was to examine more recent research about formaldehyde metabolism, pharmacokinetics, and carcinogenicity. These results indicated that formaldehyde is probably not a potent human carcinogen under low exposure conditions. Extrapolation of these research results to pediatric dentistry suggests an inconsequential risk associated with formaldehyde use in pediatric pulp therapy. (*Pediatr Dent* 2008;30:237-46)

KEYWORDS: CARCINOGENS, CHEMISTRY, FORMALDEHYDE, FORMOCRESOL, PULPOTOMY, TOXICITY

The suggestion has been made recently that formocresol use in pediatric dentistry is unwarranted because of safety concerns, and consequently, formocresol use in pediatric pulp therapy is obsolete. As a result, numerous investigations for alternatives to formocresol, some of which have shown efficacy equivalent to formocresol, have been completed. There can be no doubt that a reparative, biologic approach to pediatric pulp therapy is preferable to the absolutist, devitalization approach of formocresol pulpotomy or primary tooth pulpectomy, and research into alternatives is not only welcome but absolutely essential. This commentary will demonstrate, through a thorough review of the relevant literature, however, that the "evidence" for banning this medicament because of safety concerns has been either misinterpreted or replaced by better science.

Ubiquity of Formaldehyde

Daily formaldehyde exposure is a fact of life. Formaldehyde is found in the air we breathe, the water we drink, and the food we eat.¹ The World Health Organization (WHO)² has estimated that daily consumption of formaldehyde approximates 1.5–14 mg/day (mean, 7.8 mg/day), although daily intake from food is difficult to evaluate. Owen et al³ estimated that

North Americans eating a typical North American diet ingest 11 mg/day. There are other numerous sources of formaldehyde exposure, which are summarized in Table 1. In unpopulated areas, outdoor air contains approximately 0.2 parts per billion (ppb) formaldehyde. In populated areas with truck and automobile traffic, however, air concentrations range between 10 and 20 ppb. There have also been instances of high concentrations of formaldehyde in the air inside homes. In 2002–2003, Health Canada⁵ found formaldehyde levels of 2–81 ppb in homes in Prince Edward Island and Ottawa, Canada. Second-hand cigarette smoke might contain up to 0.4 ppm of formaldehyde.⁶ The National Institute for Occupational Safety and Health⁷ in the United States has stated that formaldehyde is immediately dangerous to health and life at concentrations of 20 parts per million (ppm) and higher.

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 At present, there are no estimates of pediatric exposure, although it is likely that children are exposed to lower amounts because of lesser food intake.

The estimated formaldehyde dose associated with 1 pulpotomy procedure, assuming a 1:5 dilution of formocresol placed on a no. 4 cotton pellet that has been squeezed dry, is approximately 0.02–0.10 mg.

Given the environmental ubiquity of formaldehyde and the recognized daily intake by humans, it is highly unlikely that

Dr. Milnes is a dentist in private practice in Kelowna, British Columbia, Canada. Correspond with Dr. Milnes at angelmanguel@shaw.ca

the elimination of the microgram quantities of formaldehyde associated with formocresol pulpotomy will have a significant impact on a child's daily exposure.

Table 1. SOURCES OF HUMAN FORMALDEHYDE EXPOSURE⁴

Atmospheric formation: Photochemical oxidation of organic compounds
Internal combustion engine exhaust
Fertilizer production
Hydrogen sulfide scavenger: Oil operations
Household products:
Dishwashing liquid
Antiseptics and disinfectants
Carpet cleaners
Carpets
Preservatives and embalming solutions
Cosmetics (maximum concentration= 0.3% v/v):
Finger nail hardeners (maximum concentration=5% v/v)
Paper products
Adhesives
Tire and rubber manufacturing
Latex paints
Resin production:
Phenolic-formaldehyde resin
Urea-formaldehyde resin
Pentaerythritol resin
Permanent press fabrics
Manufactured wood products
Forest and brush fires
Tobacco products

Pharmacokinetics of Formaldehyde

Humans produce endogenous formaldehyde as part of normal cellular metabolism. Hileman⁸ has shown that endogenous levels of metabolically produced formaldehyde range from approximately 3–12 ng/g tissue. Amino acid metabolism, oxidative demethylation, and purine and pyrimidine metabolism have all been shown to produce formaldehyde.⁹ Importantly however, human cells are physiologically equipped to manage this exposure through multiple pathways for oxidation of formaldehyde to formate and incorporation into biologic macromolecules via tetrahydrofolate-dependent, 1-carbon biosynthetic pathways. The single carbon atom released during metabolism of formaldehyde and formate is deposited in the “1 carbon atom” 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.

Cytosolic alcohol dehydrogenase, mitochondrial aldehyde dehydrogenase, and glutathione-dependent and glutathione-independent dehydrogenases are important enzymes in the metabolism of formaldehyde in hepatocytes,¹⁰ oral mucosa,¹¹ and nasal respiratory mucosa.¹² Formate is the principal oxidative product of formaldehyde, which is further oxidized to carbon dioxide and water by the action of formyltetrahydrofolate synthetase.¹³ Formate might be converted to a soluble sodium salt via alternative pathways and excreted in the urine, or it might be incorporated into the 1-carbon pool for use in biosynthesis.^{14,15}

Exogenous formaldehyde is taken up into the human body via ingestion, inhalation, and dermal exposure. Inhaled formaldehyde appears to be readily absorbed by the upper respiratory tract, but it is not distributed throughout the body because it is so rapidly metabolized.¹⁶ Ingested formaldehyde is readily absorbed by the gastrointestinal tract and exhibits little subacute toxicity after oral exposure.¹⁷ Experiments in humans, monkeys, and rats have shown no significant differences in formaldehyde concentration in the blood before and immediately after exposure by inhalation. Heck et al¹⁶ used gas chromatography and mass spectrometry 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. They showed that the blood concentrations of the 2 groups were virtually identical. In rhesus monkeys, Casanova et al¹⁸ reported that the formaldehyde concentrations in the blood after prolonged exposure to a high concentration of inhaled formaldehyde (6 ppm for 6 hours per day, 5 days per week for 4 weeks) had no significant effect on the formaldehyde concentration in blood relative to pre-exposure levels.

Human experiments have also provided compelling evidence that inhaled formaldehyde has virtually no impact on blood concentrations of formaldehyde. Heck et al¹⁶ exposed 6 human volunteers for 40 minutes to 1.9 ppm formaldehyde (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 exposure. The average formaldehyde concentration in the blood of rats, monkeys, and humans was $2.70 \pm 0.15 \mu\text{g/g}$ (mean \pm standard error) or approximately 0.1 mmol/L. In dermal studies, formaldehyde was absorbed less readily by monkeys than by rats or guinea pigs.¹⁹

The half-life of formaldehyde molecules in monkey blood is about 1.5 minutes after intravenous infusion.²⁰ A concurrent rise in formic acid levels occurs, indicating formaldehyde's metabolism.²⁰ In rats, formaldehyde's metabolism after administration via the pulp chamber is also rapid, and the majority of conversion reportedly occurs within 2 hours after administration.²¹ Exogenous formaldehyde has a biologic half-life of 1–1.5 minutes²² and is quickly cleared from human plasma. In dogs, the conversion of formate to carbon dioxide and water results in a biologic half-life for formate of about 80–90

minutes.¹³ In humans, the liver converts formaldehyde to carbon dioxide at a rate of 22 mg/min.^{3,23,24}

In mice and rats, the metabolites of formaldehyde are eliminated in urine, feces, and expired air, with the relative proportion depending on the route of administration.^{25,26} 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).²⁷

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.^{28,29} In rat and monkey tissues, however, metabolism of formaldehyde and its elimination by pathways other than DPX formation overwhelmingly predominate.³⁰

Results from dental pulp studies involving rats, dogs, and monkeys showed that formaldehyde labeled with radioactive carbon (¹⁴C) was apparently distributed among the muscle, liver, kidney, heart, spleen, and lungs. The quantities of radiolabeled chemical detected, however, were very small (1% of the total administered dose).^{21,31-33} Myers et al³² and Pashley et al³³ concluded that [¹⁴C] formaldehyde is absorbed systemically from pulpotomy sites. These studies have been widely quoted as evidence that formaldehyde is distributed to distant sites. The investigators in these studies, however, did not determine whether the labeling of tissues occurred by metabolic incorporation of the [¹⁴C] moiety of the labeled formaldehyde into macromolecules after the labeled formaldehyde molecule had been metabolized or by covalent binding (formation of protein adducts) by radiolabeled formaldehyde molecules.

In an unrelated study, Casanova-Schmitz et al³⁴ sampled the venous blood of rats after injecting either [¹⁴C] formaldehyde or [¹⁴C] formate into the tail vein. They verified that labeling of proteins and target tissues was due to metabolic incorporation of the radiolabeled metabolite of formaldehyde, ¹⁴C, and not covalent binding. The profiles of radioactivity in the blood after these injections were similar, regardless of whether [¹⁴C] formaldehyde or [¹⁴C] formate was the source of ¹⁴C. These results excluded the possibility that the labeling of macromolecules is due to formation of protein adducts by formaldehyde, because only [¹⁴C] formaldehyde is capable of forming protein adducts, whereas both [¹⁴C] formaldehyde and [¹⁴C] formate are precursors for macromolecular synthesis by the 1-carbon pool. Hence, it appears that the claims of systemic distribution in dental publications have been overstated and are, in fact, false.

Pharmacokinetics of Cresol

The second active ingredient in formocresol, cresol, has received little attention in the debate about formocresol safety or in investigations of formocresol efficacy. Cresol has poor solubility, and because of this, it has been assumed that it does not enter systemic circulation.³⁵ Cresol is highly lipophilic,

however, and has been shown to completely destroy cellular integrity, which presumably would allow for deeper tissue fixation by the formaldehyde component of formocresol.^{35,36} No data exist regarding cresol metabolism or elimination in humans or other mammals, and there is virtually no information about environmental sources of cresol to which humans might be exposed. Last, no human studies have been published that have examined plasma concentration after exposure to cresol.

A recent clinical study in Colorado has reexamined the issue of systemic distribution of formocresol.³⁷ Blood samples were drawn preoperatively, intraoperatively, and postoperatively from 30 children, each of whom received comprehensive dental treatment including at least 1 pulpotomy under general anesthesia. Blood samples were examined for formaldehyde and cresol content by using gas chromatography and mass spectrometry detection. Neither formaldehyde nor cresol was detected in any blood sample. Benzyl alcohol, however, a by-product of tricresol oxidation,³⁸ was detected in microgram quantities in a dose-response fashion in blood samples collected after placement of formocresol-containing pellets.

Benzyl alcohol is present as a bacteriostatic preservative in many multidose intravenous drugs and solutions.³⁹ It also occurs naturally in many plants, including raspberries and tea, and is an essential ingredient in many essential oils.³⁹ Benzyl alcohol is oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. It has no carcinogenic or mutagenic potential, and the allowable daily intake, as established by WHO, is 5 mg/kg.^{39,40}

Mutagenicity, Genotoxicity, and Cytotoxicity

Exposure of cells to formaldehyde leads to the formation of DPX.⁴¹ The most common types of DNA damage induced by formaldehyde are clastogenic lesions, including sister chromatid exchanges (SCEs), micronuclei and chromosomal aberrations,⁴² and deletions.⁴³ 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 modeling and prediction of formaldehyde carcinogenicity for different species.⁴⁴⁻⁴⁶ 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.^{45,46}

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 the following:

- (1) lack of detectable protein adducts or DPX in the bone marrow of normal rats exposed to formaldehyde labeled with radioactive hydrogen (³H) or carbon (¹⁴C) at concentrations as high as 15 ppm³⁴;
- (2) lack of detectable protein adducts or DPX in the bone marrow of glutathione-depleted (metabolically inhibited) rats exposed to [³H]formaldehyde and [¹⁴C]formaldehyde at concentrations as high as 10 ppm^{22,47};

- (3) lack of detectable DPX in the bone marrow of rhesus monkeys exposed to [¹⁴C]formaldehyde at concentrations as high as 6 ppm⁴⁶; and
- (4) failure of formaldehyde to induce chromosomal aberrations in the bone marrow of rats exposed to airborne concentrations as high as 15 ppm⁴¹ or of mice receiving intraperitoneal injections of formaldehyde at doses as high as 25 mg/kg.⁴⁸

Casas et al⁴⁹ have been critical of formocresol use in pediatric dentistry. They have regularly cited 2 studies as evidenced of the genotoxic and mutagenic effects of formaldehyde.^{50,51} Those published articles, in fact, represent the same study, however, with the first article reporting interim results of nasal tumor development in rodents⁵⁰ and the second (3 years later)⁵¹ reporting the final results for the same study. Although Kerns et al⁵¹ discussed formaldehyde's mutagenic potential in their animal model, they did not report results pertaining to mutagenicity, as was stated by Casas et al.

More recent research by Heck and Casanova⁵² has revealed that the development of DPX in the nasal tissues of rats and the upper respiratory tracts of primates is associated only with exposure to high doses of formaldehyde. At ambient concentrations consistent with environmental exposures, DPX are unlikely to occur. Furthermore, Quievryn and Zhitkovitch⁵³ 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. This calls into question the role of DPX in formaldehyde-induced carcinogenesis.

Cytogenetic studies⁵⁴ of lymphocytes from rodents after formaldehyde inhalation with exposures ranging from 0.5–15 ppm for 6 hours per day for 5 days failed to detect either chromosomal aberrations or SCEs at any of the formaldehyde concentrations. The authors attributed their negative results to formaldehyde's pharmacokinetics.

In vitro experiments with a Chinese hamster cell line⁴³ found that DPX and SCE, as a result of formaldehyde exposure, were associated with cytotoxicity, not mutation.⁵⁵ In addition, no mutagenesis occurred in cultured human lymphocytes below a formaldehyde threshold of 5 µg/mL in the culture medium.⁵⁶

Dental studies have not supported the contention that formaldehyde, as used in dentistry, is mutagenic. Zarzar et al⁵⁷ performed formocresol pulpotomy on 20 children by 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. Also, Zarzar et al concluded that formocresol is not mutagenic. The authors observed chromosomal aberrations in 1 (5%) of the 20 patients

but were unable to determine whether formocresol or other variables accounted for this finding.

Ribeiro et al^{58,59} reported 2 studies that assessed the mutagenic potential of formocresol as well as several other chemicals commonly used in dentistry. With a mouse lymphoma cell line, cultured human fibroblasts, and a series of formocresol dilutions 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.⁶⁰ For several reasons, however, 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, DPX's development 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

It is indisputable that cancer develops in experimental animals after inhalation of air with high concentrations of formaldehyde. 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".⁶¹ These high-dose responses, however, are unlikely to occur at sites distant from the point of initial formaldehyde contact (such as the bone marrow). This is 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.

Those opposed to formocresol use in pediatric dentistry have cited the work of Swenberg et al⁵⁰ and Kerns et al⁵¹ to support their argument about carcinogenicity. These 2 studies are, in fact, the same study, with Swenberg et al reporting interim results after 18 months and Kerns et al reporting final results for the same study 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 per day, 5 days per week for 24 months. The formaldehyde concentrations that resulted in cancer, however, were more than 1000 times the

typical human environmental exposure and 8 times the U.S. occupational exposure limit (0.75 ppm).⁶² Therefore, they are 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,^{63,64} the International Agency for Research on Cancer (IARC),^{65,66} the Agency for Toxic Substances and Disease Registry (ATSDR)^{62,67} in the U.S. Department of Health and Human Services, and the U.S. Environmental Protection Agency (USEPA).⁶⁸ 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 previously cited.

Various researchers, however, have recognized that significant anatomic and physiologic differences between humans and other animal models have confounded extrapolation of animal data to humans.^{29,69-71} Researchers at the Chemical Industry Institute for Toxicology Centers for Health Research (CIIT)^{70,71} 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 computational model, on the basis of combined rodent and primate data from the computer-generated nasal cavity airflow models, cell proliferation data, and DPX data. This model allowed them to mathematically evaluate the cancer risks associated with formaldehyde inhalation.⁷¹

Finally, with input from the USEPA, Health Canada, and peer reviewers, the CIIT researchers published a thorough evaluation of potential cancer risk from formaldehyde, integrating toxicologic, mechanistic, and dosimetric data.⁵⁵ These new experimental data, derived from sophisticated mathematical models, replaced the inaccurate default assumptions that had been used by the regulatory authorities.

On the basis of these investigations,^{55,71} CIIT suggested that cancer risk is negligible until formaldehyde exposure reaches the levels associated with cytotoxicity (in the range of 600–1000 ppb). The resulting estimates of cancer risk are many orders of magnitude lower than the 1987 and 1991 USEPA estimates.^{55,71} The model developed by CIIT overcomes problems associated with the standard risk assessment methods cited by the USEPA and the IARC.

A 2004 IARC press release⁶⁶ reclassified formaldehyde from a “probable” to a “known” human carcinogen and has been cited as evidence that formaldehyde should be eliminated from

pediatric dentistry.⁴⁹ Some clarification of the press release is required, however, or readers will be left with the impression that the IARC classification is definitive and binding. The IARC classification is not an assessment of risk but merely an attempt to answer the question of whether, under any circumstances, a substance could produce cancer in humans. Clearly, for formaldehyde the answer to this question is yes. In fact, the author requested clarification from the head of the IARC Monographs Programme regarding a threshold dosage for carcinogenicity of formaldehyde. Dr Vincent Cogliano responded “the evaluations at IARC Monograph meetings concern only whether an agent can increase the risk of cancer at some dose. We do not undertake dose-response analyses, consequently, we did not discuss a possible threshold” (personal communication, August 5, 2005).

Thus, the IARC classification serves as a hazard identification, the first step in a multilevel risk assessment process. More importantly, the IARC reclassification was based primarily on the results of a single National Cancer Institute (NCI) study⁴⁴ among workers in formaldehyde industries. That study included many workers at several plants, but only a small number of people working at a single plant were found to have a rare form of cancer. Clearly, confounding variables might have affected the results. Recognizing these uncertainties, the NCI has agreed to update the study.

Health Canada has stated that it considers the CIIT dose-response model⁷¹ “to provide the most defensible estimates of cancer risk, on the basis that it encompasses more of the available biological data, thereby offering considerable improvement over default.”⁷² The Organization for 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.”⁷³ Pediatric pulp therapy with 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 (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.”⁷⁴

The possibility that inhaled or ingested formaldehyde might induce cancers at sites distant from the respiratory or gastrointestinal tracts has been investigated in numerous long-term toxicity studies performed in rodents.⁶¹ Leukemia was not observed in any of 7 long-term inhalation bioassays in rodents, and it was not observed in 3 drinking water studies in which rodents were exposed to doses as high as 1.9–5 g/L. Leukemia was observed in a single drinking water study⁷⁵, in which Wistar rats were exposed to doses as high as 1.5 g/L. That study, however, is regarded by the Cancer Assessment

Committee of the U.S. Food and Drug Administration⁷⁶ as questionable, and the data are unreliable because of a lack of critical detail and questionable histopathologic conclusions.

Evidence from epidemiology investigations of industrial workers with exposure to formaldehyde provides 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 NCI⁴⁴ and the other from the National Institute of Occupational Safety and Health,⁷⁷ did not support a strong causal relation between formaldehyde exposure and leukemia. 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, 0.86). Moreover, a study of British chemical workers, sponsored by the Medical Research Council Environmental Epidemiology Unit in the United Kingdom⁷⁸ 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 does not support the hypothesis that inhaled or ingested formaldehyde might 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. The facts are that formaldehyde occurs naturally throughout the body, there are multiple pathways for detoxification, and only microgram quantities of formaldehyde are applied to pulp tissues during pulpotomy procedures for mere minutes. Considering these facts, 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,⁷⁹ Rolling and Thulin⁸⁰ 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.⁸⁰ A Canadian study⁸¹ of urea formaldehyde foam insulation from products in the homes of asthmatic subjects found that long-term exposure had no effect on immunologic parameters. Doi et al⁸² found that the prevalence of immunoglobulin E sensitization to formaldehyde was very low among Japanese children, regardless of whether they had asthma; furthermore, they found no clinical relevance of formaldehyde-specific immunoglobulin E. 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. Definitive data to support this hypothesis are lacking, however, 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 1:5 dilution of Buckley's formocresol is recommended. The dilution should be performed in the local pharmacy to ensure accuracy. Recent research⁸³ has indicated that a minority of pediatric dentists use diluted formocresol because it is not available commercially, so perhaps it is time for the formocresol product manufacturers to develop and market a 1:5 dilution of this medicament to replace the “full-strength” formulations now available, especially given that the effects of the 2 formulations are equivalent.⁸³

No data exist to verify the actual amount of formocresol delivered to the pulp during the performance of a formocresol pulpotomy. Results from a yet to be published study in Colorado of systemic formocresol distribution in children receiving at least 1 pulpotomy while under general anesthesia determined that the mean dose of formocresol within a cotton pellet was 0.013 mg.³⁷ This study used full-strength formocresol. Presumably, if a 1:5 dilution had been used, the mean milligram dose per pellet would have been 0.0026 mg. The actual dose that interacts with the pulp tissue is probably much smaller in both cases, however, because most of the formocresol will remain in the cotton pellet. Determining the actual doses delivered to the pulp represents an important area for further investigation. In addition, efforts are needed to disseminate information about dose delivered to both the profession and the public.

Evidence continues to accumulate that supports the successful application of indirect pulp treatment (IPT) procedures to primary teeth as well as the use of mineral trioxide aggregate (MTA) in pulpotomy procedures. A Cochrane systematic review by Nadin et al⁸⁴ in 2003 suggested that the paucity of randomized controlled trials in pediatric pulp therapy made it virtually impossible to make recommendations regarding pulpotomy procedures. Nevertheless, numerous randomized controlled trials examining both IPT and MTA have since been published. These investigations have shown that both IPT and MTA have clinical and radiographic results that are equivalent to or better than those produced by formocresol over time. The reader is referred to articles in this issue by Fuks and Coll for more detail about these promising alternatives.

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,⁸⁵ 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 all demonstrate cytotoxicity *in vitro*,⁸⁶ yet they form an important part of every dentist's restorative armamentarium. These chemicals are used in pediatric dentistry without warnings to parents and patients of the associated risks. Diagnostic radiation is an indispensable component of every dental office, yet irrefutable evidence⁸⁷ exists showing that radiation exposure can induce the development of cancers. 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.

Conclusions

Evidence presented in this review of the literature indicates that formocresol, when used judiciously, is unlikely to be genotoxic, immunotoxic, or carcinogenic in children when used in pulpotomy procedures. Until a biologic and reparative alternative has been identified that is clearly and reproducibly superior to formocresol, there are no scientific or toxicologic reasons to abandon formocresol in pediatric dentistry.

References

1. Federal-Provincial-Territorial Committee on Drinking Water. Formaldehyde: guidelines for Canadian drinking water quality—supporting documents. Available at: “www.hc-sc.gc.ca/ewh-sem/tpubs/water-eau/doc_sup-appui/index_e.html”. Accessed March 13, 2006.
2. World Health Organization. Formaldehyde: environmental health criteria 89, International Programme on Chemical Safety, Geneva, 1989. Available at: “www.who.int/ipcs/publications/ehc/ehc_numerical/en”. Accessed March 13, 2006.
3. Owen BA, Dudney CS, Tan EL, Easterly CE. Formaldehyde in drinking water: comparative hazard evaluation and an approach to regulation. *Regul Toxicol Pharmacol* 1990; 11:220–36.
4. Canadian Environmental Protection Act, 1999. Priority substances list assessment report: formaldehyde. Environment Canada, Health Canada. Available at: “www.hc-sc.gc.ca/ewh-sem/tpubs/contaminants/psl2-lsp2/formaldehyde/index_e.html”. Accessed July 22, 2007.
5. Health Canada. It's your health: formaldehyde and indoor air. Available at: “www.hc-sc.gc.ca/iyh-vsv/environ/formaldehyde_e.html”. Accessed March 13, 2006.
6. Manitoba Federation of Labour Occupational Health Centre, Inc. Formaldehyde. Available at: “www.mfloh.mb.ca/fact_sheets_folder/formaldehyde.html”. Accessed March 13, 2006.
7. The National Institute for Occupational Safety and Health. Formaldehyde. Available at: “www.tricornet.com/niosh-dbs/idlh/50000.htm”. Accessed March 13, 2006.
8. Hileman B. Formaldehyde: assessing the risk. *Environ Sci Technol* 1984;18:216a–21a.
9. Squire RA, Cameron LL. An analysis of potential carcinogenic risk from formaldehyde. *Regul Toxicol Pharmacol* 1984;4:107–29.
10. Teng S, Beard K, Pourahmad J, et al. The formaldehyde metabolic detoxification enzyme systems and molecular cytotoxic mechanism in isolated rat hepatocytes. *Chem Biol Interact* 2001;130:285–96.
11. Hedberg JJ, Hoog JO, Nilsson JA, Xi Z, Elfving A, Grafstrom RC. Expression of alcohol dehydrogenase 3 in tissue and cultured cells from human oral mucosa. *Am J Pathol* 2000;157:1745–55.
12. Dahl A. Possible consequences of cytochrome P-450-dependent monooxygenases in nasal tissues. In: Barrow C, ed. *Toxicology of the nasal passages* 1986; Washington, DC: Hemisphere Publishing, 1986:263–73.
13. Malorny G, Rietbrock N, Schneider M. [Oxidation of formaldehyde to formic acid in blood, a contribution to formaldehyde metabolism.] *Naunyn Schmiedenberg Arch Exp Pathol Pharmacol* 1965;250:419–36.
14. Bardana EJ, Montanaro A. Formaldehyde: an analysis of its respiratory, cutaneous, and immunologic effects. *Ann Allergy* 1991;66:441–58.
15. Kitchens JF, Castner RE, Edwards GS, Harward III WE, Macri BJ. Investigation of selected potential environmental contaminants: formaldehyde. Washington, DC: US Environmental Protection Agency, 1976: EPA-560/2-76-009.
16. Heck HD, Casanova-Schmitz M, Dodd PB, Schachter EN, Witek TJ, Tosun T. Formaldehyde (CH₂O) concentrations in the blood of humans and Fischer-344 rats exposed to CH₂O under controlled conditions. *Am Ind Hyg Assoc J* 1985;46:1–3.
17. Johannsen FR, Levinskas GJ, Tegeris AS. Effects of formaldehyde in the rat and dog following oral exposure. *Toxicol Lett* 1986;30:1–6.
18. Casanova M, Heck H, Everitt JI, Harrington WW Jr, Popp JA. Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. *Food Chem Toxicol* 1988;26:715–6.

19. Jeffcoat AR, Chasalow F, Feldman DB, Marr H. Disposition of [¹⁴C] formaldehyde after topical exposure to rats, guinea pigs and monkeys. In: Gibson JE, ed. Formaldehyde toxicity 1983; Washington, DC: Hemisphere Publishing, 1983:38–50.
20. McMartin KE, Martin-Amat G, Noker PE, Tephly TR. Lack of a role for formaldehyde in methanol poisoning in the monkey. *Biochem Pharmacol* 1979;28:645–9.
21. Ranly DM. Assessment of the systemic distribution and toxicity of formaldehyde following pulpotomy treatment: part one. *J Dent Child* 1985;52:4331–4.
22. Bhatt HS, Lober SB, Combes B. Effect of glutathione depletion on aminopyrine and formaldehyde metabolism. *Biochem Pharmacol* 1988;37:1581–9.
23. Waydhas C, Weigl K, Seis H. The disposition of formaldehyde and formate arising from drug N-demethylations dependent on cytochrome P-450 in hepatocytes and perfused rat liver. *Eur J Biochem* 1978;89:143–50.
24. McMartin KE, Martin-Amat G, Makar AB, Tephly TR. Methanol poisoning: V—role of formate metabolism in the monkey. *J Pharmacol Exp Ther* 1977;201:564–72.
25. Galli CL, Ragusa C, Resmini P, Marinovich M. Toxicological evaluation in rats and mice of the ingestion of a cheese made from milk with added formaldehyde. *Food Chem Toxicol* 1983;21:313–7.
26. Upreti RK, Farooqui MY, Ahmed AE, Ansari GA. Toxicokinetics and molecular interaction of [¹⁴C]-formaldehyde in rats. *Arch Environ Contam Toxicol* 1987;16:263–73.
27. Srivastava AK, Gupta BN, Gaur JS, Bihari V. Clinical evaluation of workers handling melamine formaldehyde resin. *Clin Toxicol* 1992;30:677–81.
28. Bolt HM. Experimental toxicity of formaldehyde. *J Cancer Res Clin Oncol* 1987;113:305–9.
29. Nilsson JA, Zheng X, Sundqvist K, et al. Toxicity of formaldehyde to human oral fibroblasts and epithelial cells: influences of culture conditions and role of thiol status. *J Dent Res* 1998;77:1896–903.
30. Heck H, Casanova M. The implausibility of leukemia induction by formaldehyde: A critical review of the biological evidence on distant-site toxicity. *Regul Toxicol Pharmacol* 2004;40:92–106.
31. Myers DR, Pashley DH, Whitford GM, McKinney RV. Tissue changes induced by the absorption of formocresol from pulpotomy sites in dogs. *Pediatr Dent* 1983;5:6–8.
32. Myers D, Shoaf K, Dirksen T, Pashley DH, Whitford GM, Reynolds KE. Distribution of ¹⁴C-formaldehyde after pulpotomy with formocresol. *J Am Dent Assoc* 1978;96:805–13.
33. Pashley E, Myers D, Pashley DH, Whitford G. Systemic distribution of ¹⁴C-formaldehyde from formocresol-treated pulpotomy sites. *J Dent Res* 1980;59:602–8.
34. Casanova-Schmitz M, Starr TB, Heck HD. Differentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow for inhaled ¹⁴C- and ³H-formaldehyde. *Toxicol Appl Pharmacol* 1984;76:26–44.
35. Ranly D. Formocresol toxicity: current knowledge. *Acta Odontol Pediatr* 1984;5:93–8.
36. Loos P, Hans SS. An enzyme histochemical study of the effect of various concentrations of formocresol on connective tissues. *Oral Surg Oral Med Oral Pathol* 1971;31:571–85.
37. Kahl J. Personal communication, August 2006. Available at: “<http://www.thechildrenshospital.org/news/publications/practiceupdate/2007/formocresol.aspx>”. Accessed November 12, 2007.
38. Gruber C. The pharmacology of benzyl alcohol and its esters. *J Lab Clin Med* 1923;9:15.
39. International Programme on Chemical Safety. Environmental health criteria 89: formaldehyde. Available at: “<http://www.inchem.org/documents/ehc/ehc/ehc89.htm>”. Accessed March 13, 2007.
40. U.S. Environmental Protection Agency. Integrated risk information system: tricresol (CASRN 1319-77-73). Available at: “<http://www.epa.gov/iris/subst/0030.htm>”. Accessed November 12, 2007.
41. Heck HD, Casanova M, Starr TB. Formaldehyde toxicity: new understanding. *Crit Rev Toxicol* 1990;20:397–426.
42. Merk O, Speit G. Significance of formaldehyde-induced DNA-protein crosslinks for mutagenesis. *Environ Mol Mutagen* 1998;32:260–8.
43. Crosby RM, Richardson KK, Craft TR, Benforad KB, Liber HL, Skopek TR. Molecular analysis of formaldehyde-induced mutations in human lymphoblasts and *E. coli*. *Environ Mol Mutagen* 1988;12:155–66.
44. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from hematopoietic malignancies among workers in formaldehyde industries. *J Natl Cancer Inst* 2003;95:1615–23.
45. Casanova M, Deyo DF, Heck HD. Covalent binding of inhaled formaldehyde to DNA in the nasal mucosa of Fischer 344 rats: analysis of formaldehyde and DNA by high-performance liquid chromatography and provisional pharmacokinetic interpretation. *Fundam Appl Toxicol* 1989;12:397–417.
46. Casanova M, Morgan KT, Steinhagen WH, Everitt JI, Popp JA, Heck HD. Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: pharmacokinetics, rat-to-monkey interspecies scaling, and extrapolation to man. *Fundam Appl Toxicol* 1991;17:409–28.

47. Casanova M, Heck H. Further studies of the metabolic incorporation and covalent binding of inhaled [3H]- and [14C]-formaldehyde in Fischer-344 rats: effects of glutathione depletion. *Toxicol Appl Pharmacol* 1987;89:105–21.
48. Natarajan AT, Darroudi F, Bussman CJM, van Kesteren-van Leeuwen AC. Evaluation of the mutagenicity of formaldehyde cytogenetic assays in vivo and vitro. *Mutat Res* 1983;122:355–60.
49. Casas MJ, Kenny DJ, Judd PL, Johnston DH. Do we still need formocresol in pediatric dentistry?. *J Can Dent Assoc* 2005;71:749–51.
50. Swenberg JA, Kerns WD, Mitchell RI, Gralla EJ, Pavkov KL. Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. *Cancer Res* 1980;40:3398–402.
51. Kerns WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res* 1983;43:4382–92.
52. Heck H, Casanova M. Pharmacodynamics of formaldehyde: application of a model for the arrest of DNA replication by DNA-protein cross-links. *Toxicol Appl Pharmacol* 1999;160:86–100.
53. Quievryn G, Zhitkovich A. Loss of DNA-protein cross-links from formaldehyde exposed cells occurs through spontaneous hydrolysis and an active repair process linked to proteasome function. *Carcinogenesis* 2000;21:1573–80.
54. Kligerman AD, Phelps MC, Erexson GL. Cytogenetic analysis of lymphocytes from rats following formaldehyde inhalation. *Toxicol Lett* 1984;21:241–6.
55. Chemical Industry Institute for Technology. Formaldehyde: hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation: position paper. 1999: Research Triangle Park, NC: CIIT.
56. Kreiger RA, Garry VF. Formaldehyde-induced cytotoxicity and sister-chromatid exchanges in human lymphocyte cultures. *Mutat Res* 1983;120:51–5.
57. Zarzar PA, Rosenblatt A, Takahashi CS, Takeuchi PL, Costa Junior LA. Formocresol mutagenicity following primary tooth pulp therapy: An in vivo study. *J Dent* 2003;31:479–85.
58. Ribeiro DA, Marques ME, Salvadori DM. Lack of genotoxicity of formocresol, paramonochlorophenol, and calcium hydroxide on mammalian cells by comet assay. *J Endod* 2004;30:593–6.
59. Ribeiro DA, Scolastici C, De Lima PL, Marques ME, Salvadori DM. Genotoxicity of antimicrobial endodontic compounds by single cell gel (comet) assay in Chinese hamster ovary (CHO) cells. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;99:637–40.
60. Huang TH, Ding SJ, Hsu TZ, Lee ZD, Kao CT. Root canal sealers induce cytotoxicity and necrosis. *J Material Sci Mater Med* 2004;15:767–71.
61. International Agency for Research on Cancer. Formaldehyde. *IARC Monogr Eval Carcinog Risks Hum* 1996;62:217–375.
62. US Department of Labor, Occupational Safety & Health Administration. Safety and health topics: formaldehyde. Available at: “www.osha.gov/SLTC/formaldehyde”. Accessed March 13, 2006.
63. Canadian Environmental Protection Act. Priority substances list assessment report: formaldehyde. Available at: “www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl2-lsp2/formaldehyde/formaldehyde_e.pdf”. Accessed March 13, 2007.
64. Health and Welfare Canada. Exposure guidelines for residential indoor air quality. 1987: Ottawa, Ontario, Canada: Department of National Health and Welfare.
65. International Agency for Research on Cancer. World Health Organization, Suppl 7. Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42, 1987.
66. IARC, WHO. IARC classifies formaldehyde as carcinogenic to humans: press release no. 153. Available at: “www.iarc.fr/ENG/Press_Releases/archives/pr153a.html”. Accessed March 13, 2006.
67. Agency for Toxic Substances and Disease Registry. Toxicological profile for formaldehyde: US Department of Health and Human Services, Public Health Service. Available at: “www.atsdr.cdc.gov/toxprfiles/tp111.html”. Accessed March 13, 2006.
68. US Environmental Protection Agency. Integrated risk information system. IRIS database for risk assessment. Washington, DC. Available at: “www.epa.gov/iris”. Accessed March 13, 2006.
69. Schlosser PM, Lilly PD, Conolly RB, Janszen DB, Kimbell JS. Benchmark dose risk assessment for formaldehyde using airflow modeling in a single-compartment: DNA-protein cross-link dosimetry model to estimate human equivalent doses. *Risk Anal* 2003;23:473–87.
70. Kimbell JS, Subramaniam RP, Gross EA, Schlosser PM, Morgan KT. Dosimetry modeling of inhaled formaldehyde: comparisons of local flux predictions in the rat, monkey, and human nasal passages. *Toxicol Sci* 2001;64:100–10.
71. Conolly RB, Kimbell JS, Janszen D, et al. Human respiratory tract cancer risks of inhaled formaldehyde: dose response predictions derived from biologically motivated computational modeling of a combined rodent and human dataset. *Toxicol Sci* 2004;82:279–96.

72. Environment Canada and Health Canada. Existing substances evaluation: assessment report—formaldehyde. Available at: "www.ec.gc.ca/substances/ese/eng/psap/final/formaldehyde.cfm". Accessed March 13, 2006.
73. Organization for Economic Development and Cooperation. Screening information data set, initial assessment profile. Available at: "www.oecd.org/dataoecd/24/22/31744923.pdf". Accessed March 13, 2007.
74. U.S. Environmental Protection Agency Office of Air Quality Planning and Standards, EPA Office of Air and Radiation. Rule issued under maximum achievable control technology provisions of the Federal Clean Air Act. 69 Federal regulation 18333, April 7, 2004. Fed Regist 2004; 69:18333–4.
75. Soffritti M, Maltoni C, Maffei F, Biagi R. Formaldehyde: an experimental multipotential carcinogen. Toxicol Ind Health 1989;5:699–730.
76. United States Food and Drug Administration. Indirect food additives, adjuvants, production aids, and sanitizers. Fed Regist 1998;63:35134–5.
77. Pinkerton LE, Hein M, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup Environ Med 2004;61:193–200.
78. Coggon D, Harris EC, Poole J, Palmer KT. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. J Natl Cancer Inst 2003;95:1608–15.
79. Block RM, Lewis RD, Sheats JB, Burke SG. Antibody formation to dog pulp tissue altered by formocresol within the root canal. Oral Surg Oral Med Oral Pathol 1978; 45:282–92.
80. Rolling I, Thulin H. Allergy tests against formaldehyde, cresol, and eugenol in children with pulpotomized primary teeth. Scand J Dent Res 1976;84:345–7.
81. Pross HF, Day JH, Clark RH, Lees RE. Immunologic studies of subjects with asthma exposed to formaldehyde and urea-formaldehyde foam insulation off products. Allergy Clin Immunol 1987;79:797–810.
82. Doi S, Suzuki S, Morishita M, et al. The prevalence of IgE sensitization to formaldehyde in asthmatic children. Allergy 2003;58:668–71.
83. King SR, McWhorter AG, Seale NS. Concentration of formocresol used by pediatric dentists in primary tooth pulpotomy. Pediatr Dent 2002;24:157–9.
84. Nadin G, Goel B, Yeung C, Glennly A. Pulp treatment for extensive decay in primary teeth. Cochrane Database Syst Rev 2003;1:CD003220.
85. Pumphreys RS. Fatal anaphylaxis in the UK, 1992–2001. Novartis Found Symp 2004;257:116–28.
86. Darmani H, Al-Hiyasat A, Milhem M. Cytotoxicity of dental composites and their leached components. Quintessence Int 2007;38:789–95.
87. Rice H, Frush D, Farmer D, Waldhausen J. Review of radiation risks from computed tomography: essentials for the pediatric surgeon. J Pediatr Surg 2007;42:603–7.

Conflict of Interest: Alan R. Milnes, DDS, PhD, reports no financial interests or potential conflicts of interest.

Copyright © 2008 American Academy of Pediatric Dentistry and American Association of Endodontists.

This article is being published concurrently in *Journal of Endodontics* July 2008;34:7S. The articles are identical. Either citation can be used when citing this article.