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# The Obsolescence of Formocresol

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**ABSTRACT** Concern has existed for almost 10 years regarding the safety and efficacy of formaldehyde-based medicaments like formocresol in dentistry. Formocresol has been shown to be therapeutically outdated for decades. While the use of formocresol around the world continues to drop, it still is utilized in alarmingly high rates, an age-old bias that is unsubstantiated by overall academic research. Formaldehyde remains a genotoxic and carcinogenic problem worldwide. The most recent articles are discussed in light of the need to abandon formocresol.

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This paper is intended to provide a current review of the literature, which generally reinforces the notion that formocresol is an archaic medicament and its associated applications deleterious, causing worldwide concern and a call for its elimination.[1] Yet, defense of formocresol use continues.[2]

In 1981, this author published the original compendium of research dealing specifically with the use of the carcinogens formaldehyde, cresol, and paraformaldehyde in endodontic procedures, aimed at all general practice clinicians and specialists.[3-5] The original two-year project started a debate that continues: Why haven't we eliminated formaldehyde-containing medicaments like formocresol from the dental armamentarium? The addition of cresol to the compound had only increased the deleterious effects.

Paraformaldehyde paste was also found unacceptable, both as a medicament and part of an endodontic procedure that did not utilize a full pulpectomy. An updated version of the 1981 article, published in 1998 for the millennium, reviewed separately the '80s and '90s research for carcinogenicity and the then-recent research on formocresol, adding 71 references to original 115.[6] Several letter exchanges have occurred in the journals since 1981.[7,8] The most recent ones were published in several journals.[9-13]

## Formocresol Today

Despite the hundreds of articles that have supported the mutagenicity (genotoxicity), carcinogenicity, and toxicity of formaldehyde, formocresol is still used today in full strength by an alarming number of clinicians around the world.[14] Formocresol is widely accepted for vital

pulpotomy. The simple definition of vital pulpotomy involves the surgical amputation of the coronal portion of exposed vital pulp, and the placement of a dressing over the exposed, healthy pulp stumps.

Despite the overwhelming body of research, some specialty groups still consider formaldehyde as a suitable dressing. Ninety-two board-certified pediatric dentists recently responded to a questionnaire. Of them, the vast majority, some 73 percent, still used formocresol; 28 percent were still using a full-strength formulation. The group ignored the adverse effects of formaldehyde-based medicaments.[15]

At the beginning of 2008, Dunston and Coll repeated a 1997 survey that questioned the undergraduate pediatric dentistry chairs and board-certified pedodontists who had been surveyed in 2005. Diluted formocresol was still used frequently, but was now down to 54 percent, with an increased usage of ferric sulphate and calcium hydroxide as alternative medicaments.

Clinicians should be advised that using formocresol is not recommended by the American Association of Endodontists and the American Academy of Pediatric Dentistry. Some program directors and diplomats ignore the majority recommendations and understanding of their own specialty organization.[16] Seal and Glickman have reported on the November 2007 pulp therapy symposium of those two organizations. One of the clear understandings held between those pulp therapy specialty groups, a result of chi-2 tests given before and after the symposium, is that formocresol should not be a primary tooth pulpotomy agent. Mineral trioxide is the acceptable replacement.[17]

Ironically, the formocresol pulpotomy is still the most frequently used procedure for asymptomatic caries that endangers the pulp chamber in primary teeth. Indirect pulp therapy, IPT, has been show to be an effective alternative to the full pulpotomy. Still, within the United States, the full formocresol pulpotomy remains the most popular, even though it may be obsolete and should not be the first choice instead of IPT.[18]

Dosage is also a problem. Years ago, the manufacturers of Buckley's formocresol explained to this author that the percentages listed on the packaging were an estimate and variations sold around the world could differ in its formaldehyde component by more than 10 percent. Some authors, Milnes, for example, have wrongly equated mg with ppm. 1 mg/liter is 1 ppm. Using the archaic method of squeezing a No. 4 pellet, the resulting dose estimates reported (utilizing a 1:5 dilution of formocresol) a range from .02 to 1 mg per dose.

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Authors like Milnes who defend the use of formocresol admit that the dose is clearly unknown and it remains an important area for future research.[19] Proponents of this type of methodology have never utilized reliable and reproducible studies, advantaged by a simple mean and standard deviation.[20]

Much of the supportive literature for the continuance of formocresol is supported by pharmaceutical chemists. Since formaldehyde is so prevalent in our daily lives, it matters little if we introduce a little more uncalculated dose into the systems of children. For some authors, formaldehyde released into the system poses little concern when juxtaposed against the undesirable amounts already in the food and environment.[21] Milnes, in a minority perspective, has written that since antibiotics are used frequently and cause death, why should we be concerned about formaldehyde?[19] As doctors, we should be trying to reduce the amounts of potentially harmful medicaments delivered to our patients, particularly when so many alternatives exist.

## Genotoxicity and Carcinogenicity

There is overwhelming worldwide concern about the risk of environmental mutagens and carcinogens like formaldehyde to children.[22] For decades, increases in cancer have been linked to mutagenic and carcinogenic agents. Since June 2004, the International Agency for Research on Cancer has reclassified formaldehyde as a known human carcinogen.[23] Recently, formaldehyde was strongly associated with leukemia while generally accepted as a direct cause of nasopharyngeal cancer.[24]

Despite any clinical success in its usage, it is currently accepted that attention must be paid to the mutagenic (genotoxic) and carcinogenic properties of medicaments. In early 2008, Ribeiro reviewed the need to consider genotoxicity in the hope of improving our approach to general oral health while being certain that we are not contributing to oral carcinoma.[25] Formaldehyde medicaments are capable of causing noxious activity on the actual genetic makeup of a cell. Strangely, much of Ribeiro's work with in vitro single cell gel (comet) assay indicates little if any genetic damage by formocresol, and he is quoted in recent articles.[26-28] However, Hagiwara, using Syrian hamster embryo (SHE) cells, found that the

percentages of cells with chromosomal aberrations, polyploidy or endoreduplication were increased by formocresol.

The dosage in the Hagiwara study was 14,090 times less strength than the standard used in clinical pulpotomy treatment on children.[29] Nishimura et al. demonstrated genotoxic events using .001 percent formalin — the dose of formaldehyde in Buckley's formocresol is 19,000 times greater.[30] Formaldehyde and m-cresol still show genotoxic effects to mammalian cells in other studies using SHE.[31] It is clear this area needs further study.

Liver toxicity associated with formocresol shows mixed results, depending upon the animal studies. Some rat studies have shown little if any effect on the liver.[32] In 2000, Hamaguchi showed the genotoxicity of seven dental antiseptics, among them m-cresol and formaldehyde. Again utilizing SHE, Hamaguchi concluded that both medicaments were genotoxic to mammalian cells.[33] Formaldehyde is a genotoxic substance. Studies show that formaldehyde induces DNA-protein cross-linking causing DNA lesions. Recent studies have shown that formaldehyde induces mutations in mouse lymphoma assay. Mutant colonies are created, likely by inducing chromosomal aberrations.[34]

Using human buccal cells, Lu et al. demonstrated DNA breaking and cross-linking activity. He concluded that the results of gaseous formaldehyde with the comet test indicated that formaldehyde increased the possibility of cancer at high levels.[35] The difficulty in interpreting the individual genotoxic effect of a single pulpotomy is obviously very difficult and can't be done in vivo. Looking at the peripheral blood cells of a single child who has had a formocresol pulpotomy is interesting, but studies with statistical significance would mean long-term human studies.[36] Outside of dentistry, OSHA has been making every effort to see that formaldehyde is monitored properly.[37]

The more detailed arguments at the cellular and DNA/chromosomal level are beyond the scope of this article. Multitudes of supportive research exist to make arguments based on extrapolation of data to nonrelated clinical fields, sometimes a faulty link, particularly when like dosage and exposure data are unavailable in pedodontics and endodontics. Discussion of cancer research methodologies and assays in individual medical research specialty articles should be left to other literature venues and international cancer experts, and perhaps should no longer be dissected in reviews by dental clinicians.

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## Current Pulpotomy Medicaments

For many years, clinicians have substituted a variety of medicaments for formocresol. The potpourri of historic 19th and early 20th century concoctions have often proved as effective as formocresol. Today, modern cements and chemical mixtures have been added. The use of older medicaments like zinc oxide is still being tested, with generally favorable outcomes.[38]

Caceda has developed a contemporary technique that utilizes a resin-based composite filling material — fast-setting ZOE Temrex cement, a zinc oxide and eugenol (oil of cloves) product, but still performs the formocresol pulpotomy.[39] This article illustrates the reluctance of clinicians to omit formocresol, even from newer procedures that may not require it, in this case because of the presence of ZOE.

Vargas and others haves shown success with sodium hypochlorite as a pulpotomy medicament.[40,41] Even a "green" approach exists, utilizing 19th century essential oil cinnamaldehyde, from cinnamon, with promising results in rat pulp capping when compared to formocresol.[42]

Generally, the popular medicaments are ferric sulphate, calcium hydroxide and mineral trioxide aggregate, known in the literature as FS, CH, MTA.[43] In 2008, a clinical study by Sonmez et al. found nearly equal success rates for FS as for the ubiquitous formocresol.[44] While slightly lower success rates were shown for MTA and CH, it, like so many clinical articles around the world, makes any well-meaning clinician take pause and wonder why formocresol is still the yardstick so many years after it was discredited. Sophisticated research, like that of Ng and Messer, established composite statistical meta analysis results from a broad range of pulpotomy articles that were concerned with the efficacy of MTA, formocresol, FS, and CH.

Using the established standards of clinical and radiograph success, MTA outshined formocresol, FS, and CH.[45] Moretti et al. found similar results in a controlled study that had up to 24 month follow-ups. CH showed a higher incidence of internal root resorption.[45] A light-cured version of CH did not fare as well as other studies and conditions.[47] Many studies have shown positive results for MTA when compared with formocresol.[48] Upon histological examination animal studies have shown superior results for MTA, white Portland cement (WPC), and beta-tricalcium phosphate

**TABLE 1**

**Medicaments At A Glance**

| Medicaments | Cytotoxic | Genotoxic | Carcinogenic |
|---|---|---|---|
| Formocresol | Yes | Yes | Yes |
| ZOE | Low | Low | ? |
| MTA | No | No | No |
| FS | Yes | Low | No |
| CAOH | Low | No | ? |

(b-TCP) over formocresol and FS.[49] Other promising possibilities include enamel matrix derivative (EMD), a material that utilizes active odontogenic protein.[50]

The majority of research at the present time points to MTA as the most popular choice because of its predictability in preserving pulpal health while promoting healing and regeneration of pulp tissue. Generally, MTA offers far better outcomes than formocresol, which contributes to post-treatment disease[51-54] (TABLE 1).

Recently, Bahrololoomi et al. examined the success rates of electrosurgery as opposed to the archaic formocresol pulpotomy. The failure rate in both groups did not show any statistical significance on the 70 primary molars of 5- to 10 year-olds, evidence that alternatives to medicaments should be examined and studied further.[55] Lasers, of course, are making headway as a progressive alternative to formocresol.[56,57]

## Conclusion

Revival of age-old remedies as far reaching as chicken soup are often advantageous, a well-known, effective, innocuous, and sometimes scientific adjunct for a variety of ailments.[58] The same cannot be said of long-standing formocresol due to its harmful effects and lack of scientific support.

Formocresol is very likely no longer suitable for use in dentistry, with emphasis on its applications in children's dentistry. In 2006, Fuks aptly concluded after examining a review of the pulpotomy literature from 1966-2005, "More high quality, properly planned prospective studies are necessary ..." although noted that MTA is currently the most favorable choice.[59] As many others before, Fuks reported in 2008 that suitable alternatives to formocresol exist.[60]

The decades of research have identified old-fashioned formaldehyde products like formocresol as problematic because of its toxicity, carcinogenicity, and genotoxicity. There are several viable and superior noninvasive clinical alternatives. Formocresol should be abandoned. ■■■■

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