The obsolescence of formocresol

B. Lewis[1]

IN BRIEF

- Informs the reader of the current medicaments for endodontic procedures, including paediatric pulpotomy and pulp capping.
- Updates the warnings and contra-indications for the use of formaldehyde in dentistry.
- Allows the reader to re-evaluate and choose from several newer and less toxic and genotoxic medicaments than formocresol for any type of endodontic procedure.

OPINION

Concern has existed for almost ten 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 Formocresol has been shown to be therapeutically outdated for decades.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 is still utilised 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 the light of the need to abandon formocresol.

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, defence 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 utilise a full pulpectomy. An updated version of the 1981 article, published in 1998, reviewed separately the 1980s and 1990s research for carcinogenicity and the then-recent research on formocresol, adding 71 references to original 115.[6] Several letter exchanges have occurred in 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 paediatric dentists recently responded to a questionnaire. Of them, the vast majority, some 73%, still used formocresol; 28% 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 paediatric dentistry chairs and board certified paedodontists who had been surveyed in 2005. Diluted formocresol was still used frequently, but was now down to 54%, 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 programme directors and diplomats ignore the majority recommendations and understanding of their own specialty organisation.[16] Seal and Glickman have reported on the November 2007 pulp therapy symposium of those two organisations. 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, 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, 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 their formaldehyde

[1]Former Program Coordinator in Postdoctoral Endodontics at St Luke's-Roosevelt Hospital and Columbia University, New York City and former Attending at Cedars-Sinai Medical Center, Los Angeles
Correspondence to: Dr Bradley Lewis, 934 n. Foothill Road, Beverly Hills, 90210, United States
Email: bbllewis@sbcglobal.net

Refereed Paper
Accepted 8 October 2009
DOI: 10.1038/sj.bdj.2009.1103
©British Dental Journal; 207: 525–528

component by more than 10%. Some authors have wrongly equated mg with ppm: 1 mg/litre is 1 ppm. Using the archaic method of squeezing a No. 4 pellet, the resulting dose estimates reported (utilising a 1:5 dilution of formocresol) a range from 0.02 to 1 mg per dose.

Authors 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 utilised reliable and reproducible studies, advantaged by a simple mean and standard deviation.[20]

Much of the literature for the continuance of formocresol is supported by pharmaceutical chemists and argues that since formaldehyde is so prevalent in our daily lives, it matters little if we introduce a small 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 clinicians 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 leukaemia 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 0.001 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 utilising SHE, Hamaguchi concluded that both medicaments were genotoxic to mammalian cells.[33] Formaldehyde is a genotoxic substance. Studies show that formaldehyde induces DNA-protein crosslinking 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 crosslinking 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 cannot be done *in vivo*. Looking at the peripheral blood cells of a single child who has had a formocresol pulpotomy is interesting, but work with statistical significance would mean long-term human studies.[36] Outside of dentistry, the US Occupational Safety and Health Administration (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 paediatric dentistry and endodontics. Discussion of cancer research methodologies and assays in individual medical research specialty articles should be left to other literature and international cancer experts; and perhaps should no longer be dissected in reviews by dental clinicians.

Current pulpotomy medicaments

For many years, clinicians have substituted a variety of medicaments for formocresol. The potpourri of historic nineteenth and early twentieth 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 favourable outcomes.[38] Caceda has developed a contemporary technique that utilises 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, utilising the nineteenth 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 (FS), calcium hydroxide (CH) and mineral trioxide aggregate (MTA).[43] In 2008, a clinical study by Sonmez *et al.* found nearly equal success rates for FS as for formocresol.[44] While slightly lower success rates were shown for MTA and CH, this paper, like so many 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,

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
CH(CAOH)	Low	No	?

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 outshone 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.[46] 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 (b-TCP) over formocresol and FS.[49] Other promising possibilities include enamel matrix derivative (EMD), a material that utilises 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 (Table 1).[51-54]

Recently, Bahrololoomi *et al.* examined the success rates of electrosurgery as opposed to formocresol pulpotomy. The failure rate in booth 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 are also making headway as a progressive alternative to formocresol.[56,57]

Conclusion

Revival of age-old remedies are often advantageous as 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 favourable 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 non-invasive clinical alternatives. Formocresol should be abandoned.

1. Casas M J, Kenny D J *et al.* Do we still need formocresol in pediatric dentistry? *J Can Dent Assoc* 2005; **71:** 749–751.
2. Milnes A R. Is formocresol obsolete? A fresh look at the evidence concerning safety issues. *J Endod* 2008; **34 suppl:** S40–S46.
3. Vaughan C, Stanfill S B *et al.* Automated determination of seven phenolic compounds in mainstream tobacco smoke. *Nicotine Tob Res* 2008; **10:** 1261–1268.
4. Li Y, Qu M *et al.* Genotoxicity study of phenol and o-cresol using the micronucleus test and the comet assay. *Environ Toxicol Chem* 2005; **87:** 365–372.
5. Lewis B B. Formaldehyde in dentistry: a review of mutagenic and carcinogenic potential. *J Am Dent Assoc* 1981; **103:** 429–434.
6. Lewis B. Formaldehyde in dentistry: a review for the millennium. *J Clin Pediatr Dent* 1998; **22:** 167–177.
7. Lewis B B. The formaldehyde debate. *J Am Dent Assoc* 1982; **104:** 816, 818.
8. Lewis B B. Formaldehyde in dentistry. *J Am Dent Assoc* 1993; **124:** 14, 16.
9. Lewis B B. Safety of formocresol in dentistry. *J Okla Dent Assoc* 2008; **99:** 8.
10. Lewis B B. Safety of formocresol contested. *J Calif Dent Assoc* 2008; **36:** 323.
11. Lewis B B. Formocresol use unwarranted. *N Y State Dent J* 2008; **74:** 10.
12. Lewis B B. Safety of formocresol. *J Ir Dent Assoc* 2008; **54:** 108.
13. Lewis B B. Formocresol in dentistry. *Br Dent J* 2008; **204:** 477.
14. Fuks A B. Vital pulp therapy with new materials for primary teeth: new directions and treatment perspectives. *Pediatr Dent* 2008; **30:** 211–219.
15. Yoon R K, Chussid S *et al.* Preferred treatment methods for primary tooth vital pulpotomies. A survey. *N Y State Dent J* 2008; **74:** 47–49.
16. Dunston B, Coll J A. A survey of primary tooth pulp therapy as taught in US dental schools and practiced by diplomates of the American Board Of Pediatric Dentistry. *Pediatr Dent* 2008; **30:** 42–48.
17. Seale N S, Glickman G N. Contemporary perspectives on vital pulp therapy: views from the endodontists and pediatric dentists. *Pediatr Dent* 2008; **30:** 261–267.
18. Coll J A. Indirect pulp capping and primary teeth: is the primary tooth pulpotomy out of date? *Pediatr Dent* 2008; **30:** 230–236.
19. Milnes A R. Is formocresol obsolete? A fresh look at the evidence concerning safety issues. *J Endod* 2008; **34 suppl:** S44.
20. Ruby J D. Personal communication via email. University of Alabama, Birmingham, Department of Pediatric Dentistry. 10 Oct 2008.
21. Dhareshwar S S, Stella V J. Your prodrug releases formaldehyde: should you be concerned? No! *J Pharm Sci* 2008; **97:** 4184–4193.
22. Belpomme D, Irigaray P *et al.* The multitude and diversity of environmental carcinogens. *Environ Res* 2007; **105:** 414-429. Comment in: *Environ Res* 2008; **107:** 288; discussion 289–290.
23. Cogliano V, Grosse Y *et al.* Meeting report: summary of IARC Monographs on formaldehyde, 2-utoxyethanol, and 1-tert-butoxy-2-propanol. *Environ Health Perspect* September 2005.
24. Zhang L, Steinmaus C *et al.* Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. *Mutat Res* 2009; **681:** 150–168.
25. Ribeiro D A. Do endodontic compounds induce genetic damage? A comprehensive review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; **105:** 251–256.
26. Ribeiro D A, Scolastici C. 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:** 637–640.
27. Ribeiro D A, Marques M E, Salvadori D M. Lack of genotoxicity of formocresol, paramonochlorophenol, and calcium hydroxide on mammalian cells by comet assay. *J Endod* 2004; **30:** 593–596.
28. Milnes A R. Persuasive evidence that formocresol use in pediatric dentistry is safe. *J Can Dent Assoc* 2006; **72:** 247–248.
29. Hagiwara M, Watanabe E *et al.* Assessment of genotoxicity of 14 chemical agents used in dental practice: ability to induce chromosome aberrations in Syrian hamster embryo cells. *Mutat Res* 2006; **603:** 111–120.
30. Nishimura H, Higo Y *et al.* Ability of root canal antiseptics used in dental practice to induce chromosome aberrations in human dental pulp cells. *Mutat Res* 2008; **649:** 45–53.
31. Hikiba H, Watanabe E *et al.* Ability of 14 chemical agents used in dental practice to induce chromosome aberrations in Syrian hamster embryo cells. *J Pharmacol Sci* 2005; **97:** 146–152.
32. Cortés O, Fernández J *et al.* Effect of formaldehyde on rat liver in doses used in pulpotomies. *J Clin Pediatr Dent* 2007; **31:** 179–182.
33. Hamaguchi F, Tsutsui T. Assessment of genotoxicity of dental antiseptics: ability of phenol, guaiacol, p-phenolsulphonic acid, sodium hypochlorite, p-chlorophenol, m-cresol or formaldehyde to induce unscheduled DNA synthesis in cultured syrian hamster embryo cells. *Jpn J Pharmacol* 2000; **83:** 273–276.
34. Speit G, Merk O. Evaluation of mutagenic effects of formaldehyde *in vitro*: detection of crosslinks and mutations in mouse lymphoma cells. *Mutagenesis* 2002; **17:** 183–187.
35. Lu Z-S, Yan Y *et al.* Studies on genotoxicity of gaseous formaldehyde on human buccal cells. *China Environ Sci* 2003; **23:** 566–569.
36. Zarzar P A, Rosenblatt A *et al.* Formocresol mutagenicity following primary tooth pulp therapy: an *in vivo* study. *J Dent* 2003; **31:** 479.

37. Lavoue J, Vincent R, Gerin M. Formaldehyde exposure in US industries from OSHA air sampling data. *J Occup Environ Hyg* 2008; **5:** 575–587.
38. Chédid J C, Pilipili C. A 24-month evaluation of zinc oxide pulpotomy on primary canines. *Rev Belge Med Dent* 2008; **63:** 69-76.
39. Caceda J H. The use of resin-based composite restorations in pulpotomized primary molars. *J Dent Child (Chic)* 2007; **74:** 147–150.
40. Vargas K G, Kaaren B, Lowman D. Preliminary evaluation of sodium hypochlorite for pulptomies in primary molars. *Pediatr Dent* 2006; **28:** 511–517.
41. Calderon L *et al.* Abstract of presentation at the 2007 American Academy of Pediatric Dentistry, San Antonio, Texas.
42. Gao H Y, Li W Y *et al.* Histopathology research of cinnamaldehyde as pulp-cap of pulpotomy in rats. *Hua Xi Kou Qiang Yi Xue Za Zhi* 2007; **25:** 429–431.
43. Peng L, Ye L *et al.* Evaluation of formocresol versus ferric sulphate primary molar pulpotomy: a systematic review and meta-analysis. *Int Endod J* 2007; **40:** 751–757.
44. Sonmez D, Sari S, Cetinbaş T A. Comparison of four pulpotomy techniques in primary molars: a long-term follow-up. *J Endod* 2008; **34:** 950–955.
45. Ng F K, Messer L B, Mineral trioxide aggregate as a pulpotomy medicament: an evidence-based assessment. *Eur Arch Paediatr Dent* 2008; **9:** 58–73.
46. Moretti A B, Sakai V T *et al.* The effectiveness of mineral trioxide aggregate, calcium hydroxide and formocresol for pulpotomies in primary teeth. *Int Endod J* 2008; **41:** 547–555.
47. Zurn D, Seale N S. Light-cured calcium hydroxide versus formocresol in human primary molar pulpotomies: a randomized controlled trial. *Pediatr Dent* 2008; **30:** 34–41.
48. Noorollahian H. Comparison of mineral trioxide aggregate and formocresol as pulp medicaments for pulpotomies in primary molars. *Br Dent J* 2008; **204:** E20.
49. Shayegan A, Petein M, Abbeele A V. Beta-tricalcium phosphate, white mineral trioxide aggregate, white Portland cement, ferric sulphate, and formocresol used as pulpotomy agents in primary pig teeth. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; **105:** 536–542.
50. Sabbarini J, Mohamed A *et al.* Comparison of enamel matrix derivative versus formocresol as pulpotomy agents in the primary dentition. *J Endod* 2008; **34:** 284–287.
51. Ng F K, Messer L B. Mineral trioxide aggregate as a pulpotomy medicament: a narrative review. *Eur Arch Paediatr Dent* 2008; **9:** 4–11.
52. Haney K L. Current trends in primary tooth pulp therapy. *J Okla Dent Assoc* 2007; **99:** 28–37, quiz 38.
53. Innes N. Better outcomes in pulpotomies on primary molars with MTA. Comment on: *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102:** e40–e44. *Evid Based Dent* 2007; **8:** 11–12.
54. Aeinehchi M, Dadvand S *et al.* Randomized controlled trial of mineral trioxide aggregate and formocresol for pulpotomy in primary molar teeth. *Evid Based Dent* 2007; **8:** 107.
55. Bahrololoomi Z, Moeintaghavi A *et al.* Clinical and radiographic comparison of primary molars after formocresol and electrosurgical pulpotomy: a randomized clinical trial. *Indian J Dent Res* 2008; **19:** 219–223.
56. Toomarian L, Fekrazad R *et al.* Histopathological evaluation of pulpotomy with Er, Cr: YSGG laser versus formocresol. *Lasers Med Sci* 2008; **23:** 443–450.
57. Odabaş M E, Bodur H *et al.* Clinical, radiographic, and histopathologic evaluation of Nd: YAG laser pulpotomy on human primary teeth. *J Endod* 2007; **33:** 415–421.
58. Rennard B O, Ertl R F *et al.* Chicken soup inhibits neutrophil chemotaxis *in vitro*. *Chest* 2000; **118:** 1150–1157.
59. Fuks A B, Papagiannoulis L. Pulpotomy in primary teeth: review of the literature according to standardized criteria. *Eur Arch Paediatr Dent* 2006; **7:** 64–71, discussion 72. Comment in *Eur Arch Paediatr Dent* 2006; **7:** 124.
60. Fuks A B. Vital pulp therapy with new materials for primary teeth: new directions and treatment perspectives. *J Endod* 2008; **34 Suppl:** S18–S24.