

REVIEW

A review of the effects of formaldehyde release from endodontic materials

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Abstract

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Formaldehyde is present in most living cells and the environment. In dentistry, patients may be exposed to formaldehyde through the use of several endodontic materials (e.g. AH 26) and during formocresol pulpotomies. This review outlines how the human body reacts to formaldehyde exposure, how recent data has relooked at the issue of carcinogenicity and leukaemia

associated with formaldehyde, and whether it is possible to quantify the amount of formaldehyde produced by endodontic cements. The review analyses the way formaldehyde is produced from epoxy resins and addresses the question of whether the amount of formaldehyde from endodontic cements is large enough to override the body's ability to deal with its own endogenous levels of formaldehyde and should the amount of formaldehyde produced be a concern.

Keywords: AH 26, carcinogen, endogenous levels, formaldehyde release, safety.

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Introduction

The release of formaldehyde is a widely known effect that occurs with many materials used in dentistry. Some typical examples are methacrylate and urethane dimethacrylate (base plates used in orthodontics and prosthetics), composite resin for restorations, epoxy resins used in root canal treatment and formocresol in pulpotomies (Santerre *et al.* 2001, Kopperud *et al.* 2011). Formaldehyde has been used in the manufacture of particle board, plywood, glues and foam insulation. Approximately 80% of its use is for plastic and resin manufacture. The remaining 20% is used in agriculture (seed treatment), reagents in laboratories and preservatives in cosmetics (Restani & Gali 1991).

It is important to understand the difference between formaldehyde gas and formaldehyde solution in order to avoid confusion. Formaldehyde is a flammable gas with a pungent, strong odour (at greater than 0.3 parts per million [ppm]). It is highly soluble in water (up to 55%), acetone, benzene, chloroform and ethanol. Most formaldehyde is sold as aqueous solutions, known as formalin, containing 30–50% formaldehyde with methanol as a stabilizer to prevent it polymerizing into a solid form. Formaldehyde solution is a clear colourless liquid also with a pungent and irritating odour (Lewis & Chestner 1981, Budavari 2001, Sweetman 2011). The chemical formula of formaldehyde is HCHO (or CH₂O), and it is the simplest aldehyde being a mono-aldehyde compared to the di-aldehyde of glutaraldehyde. It is a gas that dissolves easily in water to form methylene hydrate (HO-CH₂-OH). Methylene hydrate molecules react with one another, combining to form polymers with most of the formaldehyde existing as low polymers ($n = 2-8$ in the formula HO-[CH₂O]_n-H. Higher polymers

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(*n* up to 100), which are insoluble, are white powders, and these are called paraformaldehyde (Kiernan 2000). Paraformaldehyde has a formaldehyde component of 91–99%, and in liquid phase, the powder and the water vaporize at room temperature to release formaldehyde (Lewis & Chestner 1981). Formocresol was introduced into dentistry as a pulpotomy agent by Buckley in 1904 and consists of 35% tricresol, 19% formaldehyde, 15% glycerine and water. Variations include the use of a diluted formula (1 : 5) and of the mixing of the formocresol into a zinc-oxide eugenol base instead of applying the solution to the pulp on a cotton pellet (Kahl *et al.* 2008, Balaprasanna 2011).

In endodontic practice, there are materials that contain formaldehyde and/or paraformaldehyde – such as N2 paste (Indrag-Agsa, Losone, Switzerland), Endomethasone (Septodont, Paris, France), Riebler's paste (Amubarut; Wera Karl, Biesingen, Germany) and SPAD (Trailement, Quetigny, France) – which have paraformaldehyde levels between 4 and 8% (Bonsor & Pearson 2013). Other materials such as the epoxy resin cements, for example AH26 (De Trey Dentsply, Konstanz, Germany) and AH Plus (De Trey Dentsply), do not contain formaldehyde as an ingredient, but they release minimal levels of formaldehyde during their setting reaction. The formaldehyde release peaks after 2 days and then slowly decreases for a maximum period of 2 weeks (Lewis & Chestner 1981, Koch 1999).

The American Association of Endodontists issued a position paper on the use of formaldehyde- and paraformaldehyde-containing materials in which they recommended that they should not be used during endodontic treatment due to their toxicity and carcinogenicity (AAE 2013).

An electronic search was conducted using PubMed and Google Scholar search engines to identify appropriate articles written in the English language. The following keywords were used: formaldehyde, carcinogen, toxicity, formocresol, endodontics, epoxy resins, AH26, AHPlus. Textbooks such as Merck Index and Martindales were also examined for relevant information. Government agency websites in the USA, Australia and United Kingdom related to formaldehyde were examined. The reference lists of the identified publications were also examined for additional articles.

Sources of formaldehyde

The possible routes of exposure to formaldehyde are by ingestion, inhalation, dermal absorption and blood

exchange. Once absorbed, formaldehyde is very quickly broken down. Almost every tissue in the body has the ability to breakdown formaldehyde. It is usually converted to a nontoxic chemical called formate, which is excreted in the urine. Formaldehyde can also be converted to carbon dioxide and breathed out of the body. Formaldehyde is irritating to tissues when it comes into direct contact with them. The most common symptoms include irritation of the eyes, nose and throat, along with increased tearing, which occurs at air concentrations of 0.4–3 ppm (ATSDR 1999, Golden 2011).

Humans are exposed to formaldehyde on a daily basis from various sources related to lifestyle and diet. Some of these sources are foods such as shiitake mushrooms (40–380 ppm), fresh seafoods (mackerel, squid, scallop, octopus at 2 ppm), fruit and vegetables (3–22 ppm). Inhalation of trace amounts of formaldehyde can easily occur from multiple sources, such as the decomposition of plant residues, automotive exhaust, cigarette smoke, outgassing of furniture and joinery items manufactured from chipboard or plywood, insulating materials used in construction, workplace use of various synthetic resins and glues, fabrics, cosmetics and hair straightening products. Combining these various sources, the World Health Organization (WHO) estimated daily intake of formaldehyde for an adult is about 10.55 mg day⁻¹, comprising 9.4 mg day⁻¹ from food, 1 mg day⁻¹ from inhalation and 0.15 mg day⁻¹ from water (Restani & Gali 1991, WHO 2001, Tang *et al.* 2009).

Formaldehyde is present in virtually all cells in the human body as a by-product of the metabolism of serine, glycine, methionine and various other amino acids. Endogenous levels of metabolically produced formaldehyde range from 3 to 12 ng g⁻¹ of tissue (WHO 2001, Kahl *et al.* 2008). Formaldehyde can be readily detected in human plasma with typical concentrations of 2.5 ppm (Restani & Gali 1991, Lehman-McKeeman 2010, Golden 2011, Checkoway *et al.* 2012). No increase in formaldehyde concentration was seen in the blood of humans, rats and monkeys following exposure to concentrations of 1.9 ppm (2.3 mg m⁻³), 6 ppm (7.2 mg m⁻³) and 14.4 ppm (17.3 mg m⁻³) gaseous formaldehyde, respectively (IPCS 2002). This has been attributed to the deposition of formaldehyde principally in the respiratory tract and its rapid metabolism (Heck *et al.* 1985, Casanova *et al.* 1988). Exogenous formaldehyde does not accumulate in the body as it has a biological

half-life of only 1–1.5 min, and it is quickly cleared from human plasma. Such rapid metabolism would inhibit the systemic distribution of formaldehyde (Restani & Gali 1991, NICNAS 2006).

Formaldehyde is present in low concentrations (<0.2%) in a wide variety of consumer products. It is used as a preservative for the control of bacteria and fungi in water-based solutions in both industrial and consumer products including dishwashing liquids, disinfectants, fabric conditioners, shampoos, conditioners and shower gels. Many of these products are released directly into wastewater streams during their use and hence, they are a source of formaldehyde levels in water (NICNAS 2006). Some common formaldehyde-releasing preservatives include DMDM Hydantoin (1,3-dihydroxymethyl-5, 5-dimethyl hydantoin) and imidazolidinyl urea. The free formaldehyde content in DMDM Hydantoin is usually up to 2%. Any bacterial activity consumes the free formaldehyde which is then replenished from the parent compound. Over a period of time, all formaldehyde from the donor molecule is used up in preserving the product against microbes (NICNAS 2006).

Antimicrobial actions

Formaldehyde solution is bactericidal, sporicidal and virucidal, but it works more slowly than glutaraldehyde. Formaldehyde is an extremely reactive chemical that interacts with protein, DNA and RNA. When applied to unbroken skin, formaldehyde solution hardens the epidermis, renders it tough and white, and produces a local anaesthetic effect. Formaldehyde prevents tissue autolysis as it binds to protein and prevents enzymatic degradation of proteins (Kurji 2009). Diluted formaldehyde solution containing 0.75% formaldehyde w/w has been used to treat warts on hands and feet (McDonnell & Russell 1999, Kiernan 2000, Sweetman 2011).

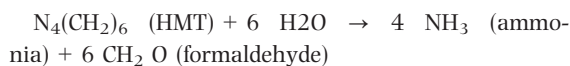
Root canal cements that produce formaldehyde on setting may allow the material to exert some antimicrobial action to counter the effects of any residual bacteria left in the root canal system at the time of root filling. Formaldehyde is a relatively nonspecific bactericidal agent, affecting the growth and viability of most gram-positive and gram-negative bacteria as well as fungi (Sweetman 2011). Formaldehyde gas has very little penetrative power as it readily condenses on surfaces and polymerizes. Its effectiveness as an antimicrobial agent requires a high relative humidity of 80–90%. Formaldehyde

gas is used for disinfection of rooms and cabinets, and it can be used with low temperature steam for sterilization of heat sensitive items (Sweetman 2011).

Some epoxy resin endodontic cements (e.g. AH 26) contain hexamethylenetetramine (HMT- also known as hexamine, methenamine or urotropine), which itself exerts antibacterial actions, and was first used as an antiseptic agent (urotropine) in 1894 (Grayson 2010). HMT is a white powder which is freely soluble in water and soluble in alcohol with an alkaline pH, but the hippurate and mandelate salts of HMT have a pH of 4 when in solution. HMT owes its antibacterial action to the release of formaldehyde which is slowly liberated by hydrolysis at acidic pH (<5.5). The hippurate or mandelate salts are also used for long-term suppression of chronic or recurrent lower urinary tract infections. It is only active in acidic urine when formaldehyde is released (Sweetman 2011). Almost no hydrolysis of HMT occurs at physiological pH, and it is therefore virtually inactive in the body at neutral pH (Scott & Wolf 1962, Sweetman 2011). The half-life is approximately 4 h, and it is rapidly and almost completely eliminated in the urine (Sweetman 2011). In humans, no harmful reactions or complications have been observed in patients receiving HMT as an antiseptic at dose levels of 4–6 g day⁻¹ for weeks (Restani & Gali 1991). HMT continues to be used as an antibacterial agent, most commonly as a food preservative because of its antimicrobial activity and its lack of taste and odour (Restani & Gali 1991). HMT is also used widely in the manufacturing of particle board, plywood and foam insulation.

Hexamine, N₄(CH₂)₆, liberates formaldehyde under acidic hydrolysis. This hydrolysis is accelerated by heating and decreasing the pH (Dreyfors *et al.* 1989, Grayson 2010). Such conditions would be uncommon following the use of root canal medicaments, but it may occur if instrumentation and root canal filling were done in one appointment and periapical inflammation was present. Therefore, the amount of formaldehyde produced when hexamine is used in a root canal filling and following a period of medicament use would most likely be inconsequential.

The chemical formula for the breakdown of HMT is as follows:



The key ingredient is the requirement of an acidic pH (< pH 5.5) (Scott & Wolf 1962, Sweetman 2011).

The controversy of formaldehyde being a carcinogen

Concerns regarding formaldehyde release are based on its known properties as an irritant as well as concerns that it may be a carcinogen. There is controversy as to the risk that formaldehyde presents as a carcinogen, and the possibility that it is a human carcinogen is impossible to exclude formally (Sweetman 2011) even though formaldehyde is not a direct genotoxic agent at sites distant to the portal of entry (nose, oral cavity) (Checkoway *et al.* 2012, Gentry *et al.* 2013). A substantial body of new evidence has appeared in the literature between 2010 and 2012, which shows no increased incidence of nasopharyngeal cancer in humans who have a mean formaldehyde exposure level of <1 ppm, up to peak levels of 4 ppm (Bolt & Morfeld 2013).

A major issue with assessing the possible carcinogenicity of formaldehyde is that it is present at relatively constant levels in the blood of humans. These background levels of formaldehyde create an analytical problem in differentiating altered or damaged DNA (adducts) that result from endogenously generated formaldehyde from those that are directly related to any exogenous chemical exposure. Various regulatory bodies have set exposure limits to formaldehyde in air (Table 1). The International Agency for Research in Cancer (IARC) has classified formaldehyde as 'carcinogenic to humans' (Cogliano *et al.* 2005), although Marsh *et al.* (2010) later showed that some of the studies on which this IARC classification was based had incomplete data sets and striking discrepancies and presented misleading evidence. The US Occupational Safety and Health Administration (OSHA) and

the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) both regard formaldehyde as a possible human carcinogen and consider that it can cause cancer in animals at high levels that are not found in the majority of workplaces.

Duhayon *et al.* (2008) stated that the most recent epidemiological studies indicate that the statement 'formaldehyde is carcinogenic to humans' is probably too strongly worded. In a review of all cohort studies published to February 2007 (Bosetti *et al.* 2008) noted that industry workers and professionals exposed to formaldehyde showed no appreciable excess risk of cancers of the oral cavity, pharynx, sinus, nasal cavity and lungs.

Logically, one would expect a site-exposure relationship with malignancies related to the tissues most exposed to formaldehyde from inhalation or ingestion. In cases of high exogenous exposure to formaldehyde, DNA effects are limited to the respiratory tract, and lesions have not been observed beyond the point of contact from inhalation exposure to formaldehyde (Lehman-McKeeman 2010) nor are levels of adducts different in remote sites. In other words, exogenous formaldehyde can cause DNA adducts in nasal epithelial DNA from direct inhalation exposure but not in bone marrow and other distant sites. The concept that inhaled formaldehyde could cause leukaemia or influence myeloid progenitor cells or other bone marrow cells have been formally excluded (Bolt & Morfeld 2013). A recent review (Gentry *et al.* 2013) concluded that there is no association between formaldehyde exposure and myeloid or lymphoid malignancies. Likewise, there is no consistent evidence of genotoxicity in the bone marrow following exogenous formaldehyde exposure (Checkoway *et al.* 2012). The

Table 1 Formaldehyde gas exposure limits from different regulatory bodies

Legal exposure limits	US-OHSA, NIOSH, HESIS	EU-SCOEL (2008)	UK-HSE (2011)	AUS-NICNAS (2006)
Threshold limit value (TLV)	0.3 ppm	0.2 ppm	N/A	N/A
Permissible exposure level (PEL) Limit (PEL) over an 8-h workshift	0.75–1.00 ppm	0.2 ppm	2.0 ppm	0.3 ppm
Short-term exposure limit (STEL)-over 15-min period	2.0 ppm	0.4 ppm	2.0 ppm	0.6 ppm
Immediately dangerous to life and health (IDLH)	>20 ppm	N/A	N/A	N/A

Data derived from Bolt & Morfeld 2013, Duhayon *et al.* 2008, and regulatory body websites. OHSA, US Occupational Safety and Health Administration; NIOSH, US National Institute of Occupational Safety and Health; NICNAS, Australian National Industrial Chemicals Notification and Assessment Scheme; HESIS, Californian Hazard Evaluation System and Information Service; EU-SCOEL, European Union-Scientific Committee on Occupational Exposure Limits for formaldehyde; UK-HSE, United Kingdom-Health and Safety Executive; TLV, FA concentration should not exceed this value at any time; N/A, not available. 1 ppm = 1 part of formaldehyde gas per million parts of air. Conversion factors (in air): 1 ppm = 1.25 mg m⁻³, 1 mg m⁻³ = 0.8 ppm (at 20 °C and 1013 hPa) (WHO 2001, Arts *et al.* 2006).

extensive metabolic capability of humans and the findings that no inhaled formaldehyde gets past nasal epithelium into the systemic circulation strongly suggest that formaldehyde should be more appropriately characterized as a chemical with adverse effects rather than as a carcinogen (Golden 2011).

Exposure limits

Formaldehyde affects humans when breathing its vapours or touching the liquid. It reacts quickly with body tissues and affects the site of direct contact (e.g. eyes, nose, throat and skin). Formaldehyde can destroy the skin's protective oils causing dryness, cracking and dermatitis. High levels (5–30 ppm) can severely irritate the lungs causing chest pain and shortness of breath (HESIS 2011). In humans, odour perception of formaldehyde (0.5–1.0 ppm) precedes sensory irritation (>2.0 ppm) of the nose, throat and eyes, with eye irritation accepted as the most sensitive end-point. Short-term exposure (<1 h) to formaldehyde below 2 ppm produces no toxicological effects on the eyes or upper respiratory tract. Moderate eye, nose and throat irritation occurs at 2–3 ppm. A formaldehyde concentration of 0.1 ppm is unlikely to result in any irritant effects for individuals, including children, asthmatics and the elderly. Adverse effects occur only at the point of contact after the concentration achieved is in excess of endogenous levels, and it exceeds the body's ability to maintain homeostasis (Golden 2011). Formaldehyde vapour is irritant to the nose, eyes and upper respiratory tract and may cause coughing, spasm and oedema of the larynx, bronchitis and pneumonia with asthma-like symptoms with repeated exposure (Sweetman 2011).

The minimum risk level (MRL) is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse, non-cancer health effects over a specified duration of exposure. For oral exposure to formaldehyde, an MRL of 0.3 mg kg⁻¹ day⁻¹ has been derived for intermediate-duration exposure, and an MRL of 0.2 mg kg⁻¹ day⁻¹ has been derived for chronic-duration exposure (ATSDR 1999).

In the blood, the mean formaldehyde concentration is reported as 2.24 mg ± 0.07 mg kg⁻¹ (Restani & Gali 1991). WHO estimates that an adult is exposed to 10.55 mg formaldehyde day⁻¹ from food, air and water. There are fairly constant endogenous levels of 2.5 ppm formaldehyde in blood (Golden 2011). Szarvas *et al.* (1986) determined the

endogenous level of formaldehyde in blood at an average of 0.5 µg mL⁻¹ of blood. With approximately 5 L of blood volume in humans, this equates to 2.5 mg of endogenous formaldehyde circulating at any one time. Endogenous turnover of formaldehyde was estimated to be approximately 878–1310 mg kg⁻¹ body weight per day, assuming a half-life of 1–1.5 min (EFSA 2014).

Quantification of formaldehyde

There are several methods used to assess formaldehyde release from endodontic materials, and each has its advantages and disadvantages (Table 2). The direct instrumental methods of GC-MS (Spångberg *et al.* 1993) and direct spectrophotometry in the infrared or ultraviolet ranges (Leonardo *et al.* 1999) can detect formaldehyde but cannot give absolute concentrations. The remaining methods involve an initial reaction with colorimetric reagents to form formaldehyde adducts which are then analyzed by their ultraviolet absorption spectra, generally after removing other components by HPLC (Cohen *et al.* 1998, Koch 1999, Koch *et al.* 2001). Current methods include direct instrumental analysis (e.g. gas phase spectroscopy using a tunable diode laser) and derivatization methods involving subsequent chromatography and ultraviolet detection, as well as more sensitive methods using fluorescence (Li *et al.* 2005). The biggest challenge with fluorescence assay methods is to avoid false positives due to the presence of contaminants or nonspecific reactions (Compton & Purdy 1980). Nevertheless, the fluorescence method when compared with the derivatization/HPLC method has been found to give statistically comparable results as well as having high sensitivity (Pinheiro *et al.* 2004).

In order to determine the amount of formaldehyde produced in a typical root canal filling, the mass of resin deposited has to be calculated. Results from three studies were used to determine the average surface area found in a prepared molar root canal (Peters *et al.* 2001, 2003, Hübscher *et al.* 2003). The average from the three studies for the total surface area of a prepared maxillary molar was 74.68 mm². Average film thickness determined from two studies (Weis *et al.* 2004, Jung *et al.* 2005), was used to determine the volume of resin and found the average film thickness was 18.0 µm. This was used in the calculation below. AH 26 was used as an example in the calculations below as this material produces the high-

Table 2 Laboratory studies of formaldehyde release from endodontic materials

Reference	Method and materials	Results	Comment
Spångberg <i>et al.</i> (1993)	GC-MS after mixing and after 100% RH exposure of AH 26 and N2	Relative FA levels from MS ion intensities. No [FA] possible but N2 level was ~1000 times that of AH 26	Method has limited quantification and easily saturated at high [FA]. Cannot be converted to ppm
Cohen <i>et al.</i> (1998)	DNPH reaction with FA then HPLC following method EPA8315. AH 26, AH Plus and EZ-Fill sonicated in pH 5 buffer at 40 °C for 60 min with DNPH	AH 26: 1347 ppm AH Plus: 3.9 ppm EZ-Fill: 540 ppm (based on mass of resin) No standard deviation given	No indication of cure time before buffer immersion. Extensive workup required before HPLC separation and detection. Sensitivity 0.25 ppm
Leonardo <i>et al.</i> (1999)	Direct UV-vis and IR spectrophotometry of AH 26, AH Plus, Top Seal and Endomethasone. Cured 72 h	FA detected in AH 26 and Endomethasone but not quantified. No FA detected from AH Plus and Top Seal	Simple UV spectrophotometry without formaldehyde derivatization is subject to interferences. IR spectrophotometry was not quantitative
Koch (1999)	Colorimetric analysis of FA with acetylacetone and ammonia using Visible spectra at 412 nm, for AH 26, Amubarut and N2. Specificity confirmed with HPLC. Effect of mix ratio, storage time and surface to volume ratio on [FA] reported	Highest [FA] initially after mixing: AH 26: 8000 ± 1800 ppm Amubarut: 70000 ± 5000 ppm N2: 17 000 ± 2700 ppm After 48 h reduced by 94% (AH 26); 61% (Amubarut) and 74% (N2)	Accepted analytical method (Hantzsch reaction). Sensitivity ~20 ppm
Koch <i>et al.</i> (2001)	FA reaction with dimedone followed by HPLC of adduct detected at 260 nm. AH 26, Amubarut and N2 analysed after 6 months storage, with grinding before analysis	AH 26: 6600 ± 2600 ppm Amubarut: 8300 ± 1000 ppm N2: 300 ± 100 ppm	Method previously used by Ruyter (1980). Variability in results may reflect sample more than method

est formaldehyde release from the epoxy resin cements. Epoxy resins such as AH 26 and AH Plus release their maximum amount of formaldehyde after 2 days. There is then a gradual decline to zero with no further release after 2 weeks.

The density of AH 26 powder, based on the above composition is 7.06 g cm^{-3} (taking the density of bismuth trioxide as 8.5 g cm^{-3} and that of hexamethylenetetramine as 1.33 g cm^{-3}). This powder is then mixed with AH26 epoxy resin (density 1.16 g cm^{-3}) at a recommended ratio of 2 : 1. The manufacturer's instructions imply measurement by volume as this is the usual mode of measurement in the dental surgery setting. Mixing to this specification gives a composition of 75% powder and 25% resin by weight and thus an average density of 5.59 g cm^{-3} .

The volume of cement will be equal to the surface area of the root canal multiplied by the thickness of the cement. Therefore, based on the above findings, the volume of cement used in a typical molar root canal filling is $74.68 \text{ mm}^2 \times 0.018 \text{ mm} = 1.34 \text{ mm}^3$.

The density is equal to the mass divided by the volume. Hence, the mass of sealer used is 7.5 milligrams (mg) in a typical root canal filling.

Cohen *et al.* (1998) used 5 g of AH 26, previously cured for 1 h and mixed it with 100 mL distilled water. This was adjusted to a pH of 5.0 to maximize the amount of formaldehyde released from the sealer. They reported that 1347 ppm was released. Unfortunately, this result cannot be converted to an amount that could be used to work out the formaldehyde levels per mg of material.

Koch *et al.* (2001) reported that the mean formaldehyde release from AH 26 was $6.6 \mu\text{g mg}^{-1}$. This material was stored dry for 6 months before ground samples were taken and analyzed. Therefore, for a typical root canal filling, the amount of formaldehyde released would be $7.5 \text{ mg} \times 6.6 \mu\text{g formaldehyde mg}^{-1} \text{ cement} = 49.5 \mu\text{g formaldehyde}$. Unfortunately, the length of time and the storage conditions mean the result is of limited value.

In another study, Koch (1999) determined that 8 mg of formaldehyde was produced per gram of

AH 26 immediately after mixing and this then reduced to $<1 \text{ mg g}^{-1}$ after 48 h. Utilizing the highest formaldehyde release ($8 \text{ mg formaldehyde g}^{-1}$), the amount of formaldehyde released in a typical root canal filling with 7.5 mg sealer would be 0.06 mg of formaldehyde, which is 1/40 of the normal endogenous levels in all humans and 1/175 of the WHO (2001) daily intake value. The formaldehyde amount falls to zero after 2 weeks as discussed earlier. The amount of 0.06 mg of formaldehyde is comparable to the daily formaldehyde intake for individuals in homes with people who smoke, which has been estimated to be 0.03–0.067 mg (Nazaroff & Singer 2004).

When performing a pulptomy, the mean dose of formocresol has been determined to be 0.013 mg per pellet, but the actual dose that interacts with the pulp is probably smaller than this (Kahl *et al.* 2008, Milnes 2008). This amount is 1/810 of the $10.55 \text{ mg day}^{-1}$ of formaldehyde that occurs in our daily intake from food, water and air (WHO 2001).

How formaldehyde is generated in the curing of epoxy resins

Epoxy resins are thermosetting polymers formed by a step polymerization with a suitable cross-linking agent such as a diamine. Because of their industrial importance, the mechanism of curing for epoxy resins has been studied in great detail to achieve optimum mechanical properties and environmental durability (Halley & George 2009). The properties achieved depend on the chemical structure of the original resin and curing agent, and the number of crosslinks per unit volume (the crosslink density) achieved in the curing process.

The curing process is a chemical reaction in which the terminal epoxide groups in epoxy resin react with a curing agent to form a cross-linked three-dimensional network. The epoxy resin cement AH26 was introduced to dentistry for root canal fillings over 50 years ago, and an unusual feature of this resin was the choice of HMT as the curing agent. HMT is a tertiary amine that, to the authors' knowledge, had not previously been in use for epoxy resin curing, but it was a key ingredient in the curing of phenolic resin precursors and in rubber vulcanization (Dreyfors *et al.* 1989). In phenolic resins, the curing reaction relies on the liberation of formaldehyde in the presence of acid.

In contrast to its use in phenolic resins, the curing reaction of hexamine with epoxy resins does not

require the liberation of formaldehyde but rather the attribute of the HMT molecule as a tertiary amine. There is no other industrial application of epoxy resins that uses HMT as a curing agent (Dreyfors *et al.* 1989), possibly because of the slow curing reaction and the likely liberation of formaldehyde if exposure to acid subsequently occurs.

It has been reported (Oliver & Abbott 1991) that moisture is required for the polymerization of AH26 (i.e. DGEBA epoxy resin cured with HMT). This is an interesting result as epoxy resin cure does not usually require the presence of moisture (Halley & George 2009) although trace amounts could potentially catalyze the reaction through a process of hydrogen bonding. The liberation of formaldehyde and ammonia by the hydrolysis of HMT is not required for it to function as a tertiary amine for catalysis of the polymerization of DGEBA epoxy resin in AH26. It is possible that an intermediate in the hydrolysis of hexamine is a primary amine, and this may accelerate the reaction so that the effect is a secondary one and not a requirement for the reaction to occur. What is important is that the HMT is a catalyst, so it is not consumed in the anhydrous curing reaction. If the cure is truly catalytic, then all HMT added to the resin is expected to be present at the end of the curing reaction.

In summary, there should be no production of formaldehyde from epoxy resins when cured with agents other than HMT. The production of formaldehyde from HMT is a consequence of subsequent hydrolysis and not the curing process of the epoxy resin in AH26.

Evaluation of the risks posed by formaldehyde release from root canal cements

Block *et al.* (1980) filled dogs teeth with N2 paste containing 6.5% paraformaldehyde and measured the amount of ^{14}C -labelled paraformaldehyde released into the circulation after 28 days. They showed that the maximum level was reached after 1 day and it was spread systemically, but there was no quantification of the amounts. In another study (S-Gravenmade *et al.* 1981), using 15% w/v formaldehyde placed in extracted human teeth, the amount of formaldehyde released through dentine and cementum into distilled water was determined. Formaldehyde penetrated readily through the apical third of roots within 60 s, particularly in roots derived from young patients. Values of 80–120 μg per 3 h were obtained after insertion of

between 5 and 10 µL into the root canal (S-Gravenmade *et al.* 1981). Taken together, these studies showed that formaldehyde permeates through dentine and cementum quickly, and formaldehyde could enter adjacent tissues and the systemic circulation. However, these materials are no longer used in contemporary endodontic practice, and their high concentrations of formaldehyde do not reflect the amount of formaldehyde that would be present in the systemic circulation when formaldehyde is released from epoxy resins (e.g. AH26, AH Plus). It is known that formaldehyde is rapidly metabolized in the human body, and this was highlighted in a study by (Kahl *et al.* 2008) involving 30 children aged 2–6 years age who underwent 85 pulpotomies (1–5 per child). A cotton pellet with 0.013 mg of formocresol was placed in the pulp chamber for 5 min for each pulpotomy performed. Blood samples were taken before and after the pulpotomies, yielding a total of 312 blood samples. There was no detectable formaldehyde above normal baseline physiologic concentrations in any of the blood samples.

In pulpotomies, formocresol is positioned in the base of the pulp chamber in a fixed area which is in direct contact with pulp tissue (for a period of 5 min). In a root canal filling, the path for formaldehyde release is more complex as the formaldehyde is produced from the epoxy resin cement which is spread throughout the entire root canal (coronal to apical). The formaldehyde has to be released and it then has to diffuse through the dentine and cementum or via the apical foramen and into the blood supply.

Systemic absorption is of no importance since after formocresol is placed and formaldehyde is produced, it vaporizes quickly and is rapidly eliminated in the urine. Vaporization and dissolution of formaldehyde in exudate minimizes the potential toxicity of root canal medication (Gutierrez *et al.* 1991).

Appraisals of risk from formaldehyde

The authors of two older articles (Lewis & Chestner 1981, Lewis 1998) have presented a view on formaldehyde which is not consistent with the more recent reports of measured formaldehyde release from dental materials used *in vitro*. These earlier articles discussed chronic exposure of high levels of formaldehyde rather than the short-term exposures used for formocresol pulpotomies (i.e. minutes), and the doses from epoxy resins in root canal fillings that are at least 40-fold lower than those normally ingested or present

in the circulation. There is no current evidence of harm in humans from the latter (Sue Seale 2010). This same confusion is evident in a paper from the same author (Lewis 2010) which claims that 'recently formaldehyde was strongly associated with leukaemia whilst generally accepted as a direct cause of nasopharyngeal cancer'. The research on formaldehyde referred to in that paper has for the most part been discredited or updated, primarily because newer and more rigorous methodologies have been used to investigate formaldehyde (Milnes 2008).

In conclusion, it appears that the amount of formaldehyde released during pulpotomies with formocresol and from resin-based root canal fillings are at least 1/40 less than the normal endogenous levels in humans, and they do not pose any health risks.

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