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**Long-term evaluation of root amputated anterior teeth
after preoperative root canal filling with N2 and gutta-percha points**

Inaugural dissertation
in fulfillment of the requirements for the degree of
Doctor of Dental Science (DDS)

of the Faculty of Human Medicine of the
Johann Wolfgang von Goethe University
Frankfurt am Main / Germany

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Holzerath, Germany

Frankfurt am Main, 1998

1. Introduction and aims

Next to the tooth extraction, root amputation is one of the standard surgical procedures which are considered an established method in addition to conservative endodontic root canal treatments, especially for anterior teeth. In compliance with strict indication, it offers a 90 % possibility to save a tooth for many years to come.

The surgical procedure itself primarily consists of the removal of the root tip with apical ramifications, and the removal of periapical inflammatory tissue. Regarding procedure and choice of root canal filling materials, there are various recommendations and evaluations. Where root canal filling materials are concerned, the same requirements as for preserving endodontic surgery are applicable; they must be tissue-friendly and parietal to separate the canal from the resection wound as bacteria-tight as possible. Besides that, they must not be absorbable, shrink, or become porous.

Apicectomies, which were preoperatively root filled with N2 and gutta-percha points, were mainly re-examined for this study. A variety of scientific opinions and comments are available in reference to N2, and the content of paraformaldehyde contained in N2 has increasingly become the bone of contention over the last years. Fact is, however, that this root canal material was used in many practices in the past and is still used today, especially in the USA.

Aim of the work at hand was to evaluate resection healing of preoperatively root canal filled and finally resected teeth years later through clinical and radiographic follow-up examinations, and in this process to determine probable dependencies on various factors and to compare these findings with other authors. Furthermore, the healing results of preoperatively with N2 and gutta-percha points filled and resected teeth are to be compared not only with other follow-up examinations, in which a different sealer than N2 was used,

but also with my own apicectomies, for which the preoperative root canal filling with unknown materials used for the resection was not examined.

For this purpose, between October 1995 and August 1996 I conducted some clinical and radiographic examinations of apicectomies on mandible and maxillary anterior teeth, which were carried out in my practice between October 1983 and October 1995, both following my own preoperative root canal fillings with N2 and gutta-percha points, and after leaving the existent root canal filling with unknown materials in place.

2. Material properties and tissue compatibility of N2

N2 is composed of:

- 100 g of powder contain: 63.0 g zinc oxide, 3.6 g titanium oxide, 10.0 g bismuth sub carbonate, 15.0 g bismuth sub nitrate, 7.0 g paraformaldehyde, and 1.4 g red lead
- 100 g of liquid contain: 77.0 g eugenol, 1.8 g rose oil, 1.2 g lavender oil, and 20 g peanut oil.

In the USA, N2 is referred to as RC2B (generic formula). It is available in a minimally modified composition; instead of 7.0 g of paraformaldehyde it contains only 6.5 g paraformaldehyde.

Formaldehyde is a colorless and pungent smelling gas, germicidal and well soluble in water. A 35 % aqueous solution is referred to as formalin. Next to ring structured compounds, formaldehyde also forms long-chained polymers = paraformaldehyde. Formaldehyde owns the general properties of all aldehydes. It is reductive and easily oxidizable. It reacts with ammonia and ammonia derivatives and also with protein, which contains the amino group (-NH₂). Together with protein, formaldehyde forms solid, hard condensation products, whereby the protein gets tanned and microorganisms are destroyed. The hardening of the cell wall prevents further cell divisions and thus their reproduction. Formaldehyde reacts in the same manner with any protein-containing tissues, with blood, pulp tissue and the periapical tissue. Formaldehyde is also used to harden microscopic preparations [85, 87, 105].

Aldehydes result from oxidation (dehydration) of primary alcohols. The term "aldehyde" is the abbreviation of "alcohol dehydrogenates" = dehydrated alcohol. Formaldehyde (also referred to as methanol) is the simplest aldehyde. Its chemical formula is H-CHO or CH₂O.

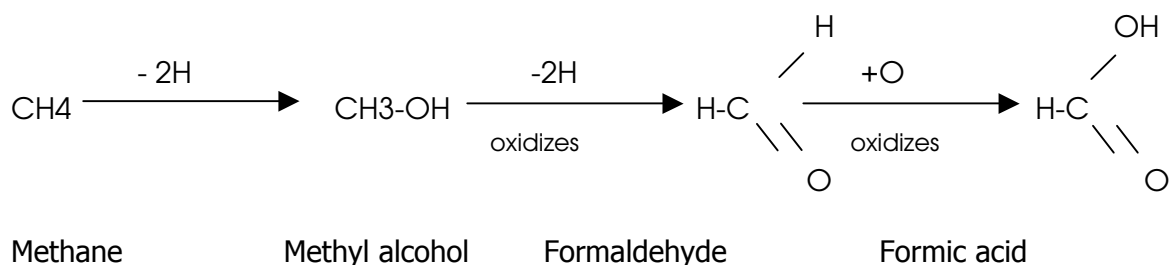


Fig. 2.1 Formation of formaldehyde

The formaldehyde contained in N2 powder is chain-linked in the form of paraformaldehyde. According to the manufacturer, the content is 7 % in freshly produced powder. The content is reduced to 4.7 % in the powder/liquid mixture [105].

According to *Orban*, formaldehyde is already used since 1894 in dentistry, initially for pulpitis treatment, later for pulp amputations, gangrene treatment, as devitalization agent, for gingival treatment and as a component for temporary and definite root canal fillings. And since that time the substance is just as controversially discussed as is amalgam [83].

In 1905, Formocresol, which contains formalin, respectively formaldehyde, was popularized in the USA as medical and disinfectant root canal insert by *Buckley*. Formocresol is a combination of cresol and formalin, which contains formaldehyde, glycerin, aqua dest and orthocresol (= phenol compound: 2-methyl phenol). Formocresol is a very strong disinfectant, because cresol alone is three times as efficient as phenol, and even though it causes less necrosis, it nevertheless precipitates protein on its own [105]. Due to its high clinical success rate, the pulpitis coronal therapy with Formocresol in the primary dentition is still considered standard therapy in 2008, especially in the Anglo-American region. For direct primary pulp capping, *Einwag* recommends an initial 5 minute application of a Formocresol solution, followed by the application of a mummification paste consisting of a drop of Formocresol and eugenol each mixed with zinc oxide powder, and finally the lining and restoration. This so-called "5 minute Formocresol technique" has gained acceptance world-wide and is still used today [147].

Beyond dispute is the powerful antimicrobial effect of formaldehyde. For decades it was used for surface disinfecting and gas sterilization. Opinions regarding the optimal formaldehyde dosage as therapeutic pulp agent differed for years, until the Hungarian *Orban* tested the dosage effect in 1934 [83].

By adding some paraformaldehyde to temporary filling materials, *Orban* ascertained reduced dentin sensitivity, and in the course of time a secondary dentin formation after a few days of retention, if the insert with a concentration of 5 - 20 % remained in place for just a few days. Secondary dentin formation, which was localized at lower dosage and diffused within the entire coronal part of the pulp, was observed in dogs after three to nine months while using paraformaldehyde Aquadont inserts with a concentration of 1 - 5 %. A 20 - 50 % formaldehyde Aquadont concentration led to bleeding and inflammations with every aspect of defense reactions of the tissue.

Thus *Orban* came to the conclusion that the positive effect of formalin solely depends on concentration and dosage, which should be at the range of 5 % to heal sufficiently without toxic effect [83].

Based on this limited dosage, *Sargenti* and *Richter* introduced the N2 root canal filling material in 1954.

Additional formaldehyde-releasing root canal filling materials available are for instance AH26 and Riebler, and until a few years ago also Endomethasone. The succeeding product, Endomethasone N, does not contain formaldehyde any longer.

Although AH26 releases formaldehyde, which happens by reaction between resin and hardener, the material is recommended by many authors and universities. N2, however, is subject to increased and constant criticism for its formaldehyde content [33].

The formaldehyde content in N₂ or other formaldehyde containing materials should be considered in relation to other circumstances during which people inevitably come in contact with formaldehyde. Formaldehyde is contained in various commodities, tooth pastes, mouth washes, cosmetics, nail polish removers and so on. Formaldehyde is present everywhere in our ecology and in the air we breathe. It also is a normal metabolite caused by adrenalin decomposition, and it is present in small quantities in our human cells. The human organism metabolizes formaldehyde very quickly [88].

In 1993, *Christensen* writes a letter published in the "Newsletter of American Endodontic Society": "... many other (dental) medicaments, cements ... and other materials have significantly more toxic potential. Even some foods contain agents that are more dangerous. Clinical success is the final research test" [94].

The WHO published the following numbers on the topic of environment and formaldehyde in 1989:

Formaldehyde content in comestibles in mg/kg:

- 60.0 in pears
- 17.3 in apples
- 6.7 in carrots
- 5.7 in tomatoes
- 20.0 in pork
- 8.0 in sheep meat
- 20.0 in sea fish (smoked)
- 20.0 in cod
- up to 3.3 in cow's and goat's milk
- up to 3.3 in cheese products

Formaldehyde content from the environment in mg/day:

- 0.02 from ambient air
- 0.5 - 2.0 from indoor air
- 1.5 - 14 from food (adults)
- 0.1 from drinking water
- 1.0 from smoking (20 cigarettes)

According to the WHO, the aerosol concentration in Deuselbach was measured at 40.9 +/- 26,0 ng/m³ from 1974 to 1976. The formaldehyde content of the air is mainly an intermediate product which results from the decomposition of CO₂ and CO [88].

According to the WHO, the rain water concentration in Mainz was measured at 0.174 +/- 0.0185 mg/l from 1974 to 1977.

In comparison to the WHO numbers:

A root canal, which was prepared to a width of 50, holds approximately 50 mg of N₂. The amount of 50 mg of N₂ would correspond to approximately 2.5 mg of paraformaldehyde. By utilizing the gutta-percha method, this amount would be significantly reduced by 10 - 20 % = 0.25 - 0.5 mg of paraformaldehyde. The relation to commodities and other WHO values is remarkably low, particularly because the question arises whether 0.25 or 0.5 mg of formaldehyde would actually be completely released. *Maschinski* provided evidence that

paraformaldehyde as powder component may release close to half the formaldehyde contained therein, but that the powder-eugenol mixture does not release formaldehyde, because formaldehyde reacts with phenol and its derivatives, and that formaldehyde is bound depending on the phenol content of mixtures. In his tests, however, 10 % of the paraformaldehyde content of the devitalization paste Toxavit, and 5 % of Asphalin as representative of temporary inserts, were released [81].

Furthermore, the test results of individual material components do not necessarily point to the properties of the entire material composition. If two components, such as powder and liquid, are mixed, the properties of individual components will be changed while the material hardens. For that reason, no indication of N2 allergies can be found, although N2, as well as other root canal filling materials, contain components with allergenic potential.

Regarding definition, toxicity must be distinguished from tissue irritating effects of a substance. Toxicity originates from the interaction between a chemical substance and a biological relevant macro molecule. Tissue irritating properties on the other hand are caused by various reasons. Both biological properties may be subdivided according to their pathologic findings, such as:

- cytotoxic
- inflammable
- allergenic
- carcinogenic effects [102].

Moreover, the systemic effect, whose biologic reaction does not occur at the application site, but only once the pertaining substance is transported through the organism, must be distinguished from the local reaction, which occurs right at the application site.

When it comes to dental materials, reports concern primarily the cytotoxic, locally inflammable, or contact allergenic effects; there cannot be any doubt, though, that other possibilities of harm, mainly the carcinogenetic effect of dental materials, may play a role.

Examination regarding systemic toxicity:

This covers various methods of determining the lethal dose = LD50, which describes the amount of substance killing 50 % of a number of laboratory animals. This value represents the extent of toxicity of chemical substances, which is required for approval of such substances according to the Chemicals Act. The higher the LD50 dose, the better it is for the pertaining substance and its non-toxicity. The relevance of LD50 values is, however, strongly limited, as most of these orally administered, hardened substances show LD50 values over 2 g/ kg of body weight and thus are not considered toxic [102].

The LD50 dose for the American RC2B is 5900 mg/kg, and for some other substances as follows:

- | | | |
|------------|--------|------------|
| - Eugenol | LD50 = | 2680 mg/kg |
| - Salt | LD50 = | 3000 mg/kg |
| - Aspirin | LD50 = | 815 mg/kg |
| - Caffeine | LD50 = | 127 mg/kg |
| - Nicotine | LD50 = | 24 mg/kg |

Provided that a root canal holds an average of 50 mg of filling material, as measurements have shown, the LD50 dose for an 80 kg human would only be reached if 10,720 root canals

were filled with 50 mg of RC2B each. Systemic toxicity is thus impossible for RC2B and also for its German variant N2, due to its almost identical composition [136].

The excellent physical properties and strong antibacterial effect of N2 are hardly challenged. The stumbling block is and remains its paraformaldehyde content.

Sargenti describes the effect of the N2 root canal filling material that he introduced together with *Richter* in 1954 as follows: "N2 forms an immediate immobilizing barrier of residual pulp tissue at the physical foramen by immobilizing, respectively scabbing a layer of pulp cells directly after its insertion. This well-defined membrane, also termed sclerotic zone, is supposed to establish further contact to the remaining pulp tissue, but not to the N2. At the same time, canal walls and ramifications are impregnated and hermetically closed. Under the scabbed zone and within the pulp tissue the biologic healing, involving the formation of hard substance or connective tissue scabbing, takes place within the hardening phase. Cementoid and dentoid tissue develops at the canal walls of the residual pulp. N2 is not absorbable in the canal and adheres well to the canal walls. It owns a lasting antiseptic action, mainly against staphylococcus, streptococcus, and coli bacillus. Immediately after mixing, this action is most pronounced, then it slowly declines, and remains stable for a long time with less effect." [71].

Some of the various statements and evaluations about N2 and other formaldehyde-containing root canal filling materials are outlined below:

Physical properties:

Considering the overall results and the comparison with the root filling materials Diaket and phosphoric cement, which were examined as well, *Hetwig* clearly concluded in 1958 that N2 comes closest to meet the physical requirements made on a good root filling material. It showed to be insoluble in water, non-porous, of perfect marginal fit, and it was even able to bind minor amounts of liquid, which is of added benefit in case of not entirely dry root canals, in his opinion [16]. Other authors, who evaluated the material later on, confirmed the excellent marginal fit and non-absorbability as well [18, 89].

Antimicrobial action:

Grossman tested eleven root canal cements regarding their antimicrobial action via agar-agar diffusion method aerobically. The experiment showed that N2 or RC2B executed a higher degree of bacterial inhibition than pure zinc oxide eugenol cements or synthetic cements, due to their formaldehyde content. The antibacterial zone of N2 or RC2B were nearly twice as large as those of the others. Most zinc oxide eugenol based cements just showed a minor antimicrobial effect after 5 days, while paraformaldehyde containing cements had a significantly reduced, respectively no antimicrobial effect after only 10 days. The author attests the paraformaldehyde cements noticeable antimicrobial effect" [91]." Further examinations of 28 root canal sealers, cements and pastes - amongst them AH26, Endamethansone, Diaket etc. - by *Orstavik* also showed N2 to own the best antibacterial properties in any test series, and that no difference in the antimicrobial effect could be detected between pure ZnO eugenol and ZnO eugenol + paraformaldehyde containing preparations from day 28 on. During the first 7 days, however, the ZnO eugenol + paraformaldehyde containing preparations had a stronger antimicrobial effect [148].

Tissue compatibility and toxicity:

Histological examinations conducted by *Palazzi* showed that N2 induced cell coagulation at the contact area of N2 / residual pulp tissue after 16 to 26 days, similar to the sclerotic zone

described by *Sargenti*. Following another 2, 3, 6 and 9 month, the histological sections of human teeth showed intact periapical tissue [150]. During similar examinations after 2 month, 4 years and 5 years, *Schönherr und Bauer* found biological healing with significant secondary dentin formation at the apical residual pulp and cement at the apical foramen, but no inflammable changes in any case [149]. The histological sections taken by *Rowe* also show after 1/2, 1 and 2 years that N2 root fillings were well tolerated by vital residual pulps and that calcification, which leads to biological healing, took place within the canal. Because there are no signs of inflammation at all, the author presupposes that the presence of a minor formaldehyde amount does not have an irritating effect on the residual pulp and does not disrupt the restorative processes, but rather exerts a stimulating effect on the biological restoration [92].

Examinations conducted by *Friend and Browne* showed severe tissue reactions during the first 2 - 4 days following the implant of N2, AH26 and Diaket into the subcutaneous tissue. A necrosis of variable size developed, infiltrated by polymorphonuclear leukocytes with some plasma cells and lymphocytes. The strongest initial reaction was caused by Diaket and AH26. N2 reached a new maximum after 7 days and leveled off thereafter. After the use of AH26, the initially sustained powerful tissue reaction leveled off entirely after 3 month, after the use of Diaket and N2 it persisted in a heavily diminished state for up to 12 month [90]. *Neugebauer, Albers and Bull* assessed retrograde root fillings in animal experiments and discovered that N2 also left noticeable signs of tissue intolerance, although not to the extent as for amalgam, which was assessed in this context. N2 did not show any radiographic modification processes, displayed an absorptive and connective tissue related bone modification, and no fluorescence-microscopic formation. A connective tissue related reaction is strictly considered an inferior substitute. However, in view of necrotizing properties, this is to be considered a positive reaction after all and thus desirable in addition to the ossification. The authors consider the formaldehyde addition in N2 responsible for the poor tissue compatibility [18].

During a 90 day study regarding the biologic stability of the materials, necrotizing effect, inflammable reaction, and tissue changes at the contact area, *Muruzabal and Erasquin* assessed the root filling materials Hermetic, Mynol, N2, Kerr, Minium-Eugenol and ZnO-Eugenol on underfilled, correctly filled and overfilled molar fillings of rats. Regarding the material stability at the surface, N2 as well as AH26 were found at good medium range. Titanium oxide, which is contained in both materials, is considered cause of this result. N2 displayed the strongest necrotizing effect, which may result from the formaldehyde that quickly diffuses into the tissue. The effect on bone and root cement lasts merely a few days and leads to reactive ankylosis due to increased bone and cement formation. When it comes to inflammable reaction, N2 and ZnO-Eugenol were found at medium range. The worst material was Hermetic. Regarding tissue changes at the contact area, N2 was found at medium range of all tested materials and showed connective tissue encapsulation without inflammatory infiltrate after 30 days. In case of overfilled material, the capsule was surrounded by bone lamella, and bone formation was observed after 90 days.

Klaiber et. al. carried out toxicity tests on root filling materials, amongst them N2, Diaket, AH26, Endomethasone, Aptal-Zinc Resin, Hermetic and their individual components, during which Diaket and AH26 were found to be the most toxic materials, followed by Hermetic with only marginally better results. N2, Aptal-Zinc Resin, and Endomethasone (which included the paraformaldehyde component at the time) were ranking the next best results, whereas N2 was found at medium range within this group. Altogether, this group did not display a tissue compatible behavior, but nevertheless a noticeably diminished cytotoxic remote effect compared to previously mentioned materials. Furthermore, these tests revealed the strongly cytotoxic effect of eugenol [7]. Then *Heidemann and Lampert* tested N2, Diaket, AH26 and Endomethasone amongst others, at which the most toxic effect on cell cultures was caused

by Diaket, the material that damaged cells severely. The next material in line was N2, followed by AH26, and finally Endomethasone, whereas Endomethasone still included the paraformaldehyde component at that time. The authors specifically point out the contrast to the clinical experience, at which especially Diaket and AH26 have proven as established filling materials, although they had attributed significant cell reactions to both materials [19].

Langeland et. al. assessed the use of N2 on rats, apes and humans and came to the conclusion that N2 initially creates remarkable and long-lasting inflammatory reactions of periapical tissues, leads to internal and external resorption and supports dystrophic calcification, so that N2 is far-off from not being an irritant at periapical tissues [86]. During the examination of various root filling materials on test animals, *Langeland* observed acute and chronic inflammation of periapical tissues that had contact with N2, and furthermore hard tissue resorption and apposition at the dental pulp and canal walls. The likewise tested gutta-percha points (DeTrey and Premier) were also found to be toxic [74]. *Schmalz* explains that during all biologic examinations, such as cell and tissue cultures, subcutaneous implantation and injections on test animals, N2 was displayed the highest local toxicity compared to root filling materials such as gutta-percha, chloro-percha, AH26, Endomethasone and Diaket. He emphasizes though that this type of toxicity test delivers merely biologic basis information, but does not provide evidence regarding possible qualities for the use on patients. During practical tests, however, he detected necrosis at cement and bone areas, which were generated by N2, and sees the cause for this "enormous toxicity" in the combination of paraformaldehyde and corticoid, as paraformaldehyde in the concentration in which it has the desired disinfectant impact, also displays a toxic effect. He solely recommends the pastes AH26 or chloro-percha for cementing gutta-percha points [102]. Despite the content of hexahydrobenzol tetramine powder in AH26, which is connected by formaldehyde and ammonia, *Geurtsen* and *Leyhausen* consider it a given fact that formaldehyde-containing ZnO sealers, and especially N2, hold a high and long-term cytotoxic potential, because N2, unlike AH26, contains some aromatic oils with cytotoxic effect next to eugenol, and because the formaldehyde release from the epoxy-resin sealer AH26 occurs just maximally 2 days after mixing, and to a lesser content compared to N2 [101].

Not least result from this the various statements regarding clinical and clinical radiographic evaluation of N2 or other formaldehyde-containing materials used on patients: While *Miller* observed considerable and speedy bone formation in case of N2 root fillings followed by apicectomies and received the impression that N2 exerts an osteogenetic effect, *Bernhöft et. al.* achieved a success rate of only 62.4 % with N2, compared to 84.2 % with gutta-percha, while they conducted clinical radiographic examinations of various root filling materials. The overstepping of root canals with N2 led to a 100 % failure compared to only 22.5 % with gutta-percha [17, 82]. *Einwag* generally termed the application of formaldehyde seceding products such as Formocresol and N2 for instance for the treatment of diseased deciduous tooth pulps (mortal amputation, vital amputation) as an equally practical and successful method with a virtually all-embracing range of use. During his own studies, he was able to confirm the high success rate of other authors regarding the use of Formocresol as enclosed temporary insert in case of e.g. gangrene and apical periodontitis, which prevents an adverse "left open" condition. Regarding N2, he explains that this material does neither differ from Formocresol in respect of clinical success rate nor in respect of its histological effect, so that a differing behavior is not to be expected considering the similarity of effective agents, formaldehyde in Formocresol and paraformaldehyde in N2, and the conformity of the carrier substance ZnO eugenol. A similarly safe and practical alternative to formaldehyde seceding products would currently be glutaraldehyde at best. Despite encouraging data regarding glutaraldehyde and the long-lasting discussion about possible side effects, only 29.6 % of 125 consulted universities world wide consider to convert the Formocresol method in favor of glutaraldehyde [147].

Systemic effect and carcinogenicity

According to *Geurtsen* and *Leyhausen*, a cytotoxic or even mutagenic effect must frequently be considered during and after the use of endodontic filling materials with strong antibacterial action. Although N2 and Diaket were not found to be mutagenic during salmonella/microsome tests, N2 evoked some changes in the umu tests and DIT, which are relevant for genotoxic activities as well. It must be clarified through further studies if eugenol, the mutagenic formaldehyde, or both substances are responsible for this effect, especially because eugenol was definitely found to be genotoxic during various in vitro tests. Apart from that, contrary to the antibacterial effect it was found that the use of ZnO containing sealers may cause aspergillosis of the maxillary antrum after overfilling maxillary molars. This shows that a material, which inhibits certain species, may nevertheless support the growth of certain microorganisms [101].

In their report about formaldehyde, the WHO reports summarizes that an international commission assessed the carcinogenic risk in 1981 already and updated this information in 1987 with the conclusion that only limited evidence is present to substantiate this carcinogenicity for humans. In previous pages, the WHO reports about a number of tumors, but that a causal connection with formaldehyde does likely just exist for nasal and nasopharyngeal tumors in case of pertinent exposition [88].

According to *Maschinski*, the German scientific community ranked formaldehyde amongst the substances suspect to have carcinogenic effects, after they exposed rats to formaldehyde concentrations of 5 to 15 ppm over a period of two years. This suspicion was not epidemiologically confirmable for humans after 2.500 persons, who occupationally used or processed formaldehyde, were examined without detecting an increased occurrence of tumors on both nose and lung. The maximum workplace concentration value is 1.00 ppm. Most people are exposed to formaldehyde concentrations of 0.01 ppm at polluted areas, and/or 0.5 ppm caused by passive smoking every day [81].

During one study, the precipitation of C14-charged formaldehyde, applied as Formocresol into the root canals of cats, was measured. At first on the basis of the C14CO₂ contained in the breathable air and 72 hours later in the animals' blood and urine. All animals were sacrificed, and lungs and livers were examined as to C14 content. C14 was found to be present everywhere, but in a very low percentage of the total dose per organ. In addition to that, no significant difference was found between the group that was supplied with larger Formocresol portions and those with smaller ones. The authors came to the conclusion that apart from various metabolisms of different animal species, formaldehyde diffused and metabolized very quickly during this experiment [96].

Maschinski comments his tests, which are contradictory to the examinations conducted by Block et. al., who applied an as radioactive marked C14 paraformaldehyde equivalent to the N2 composition with an activity of approximately 10 to the power of 10 Becquerel into the root canals of test animals, and subsequently verified a falling tendency down to the range of approximately 10² Bq/g in blood and lymph nodes, that in his opinion not more than maximally one hundredth of the applied amount of paraformaldehyde was released. Considering the fact that in a root canal, which holds a volume of just few mm³ and has a contact area of less than 1 mm² to the vital tissue, if any formaldehyde would be released at all, it could just be a very small amount, which means the aspect of some damage caused by some formaldehyde containing materials is not relevant any longer [81].

The president of the "American Society of Toxicology", *Jeffrey Brent*, testified as sworn expert on the occasion of a court hearing on January 8th, 1997 in Wichita Falls, Texas

(according to Hyatt Court Reporting, File No. 7-95-CV-057-X dated January 8th, 1997): "N2 is no more toxic than any other root canal filling material. N2 possesses no mutagenic or carcinogenic potential. A study, during which formaldehyde was charged with radioactive C14 prior to its application, reportedly proved that C14, through intense C14 activity, was still detectable in other body parts, from which it was erroneously concluded then, that paraformaldehyde was transported into these body parts accordingly. But what was transferred in reality was just C14" [100].

In summary, the results of histological studies regarding cytotoxicity and mutagenicity/genotoxicity should make us weight the usefulness of the materials in view of undesired properties against the threat to human health. It certainly is very difficult to determine whether a failure resulted from the cytotoxic activity of a material or from remaining microorganisms, and what exactly led to failure. Adverse material effects, however, may play a major role in many failures, for which significant fault cannot be found in the preparation. For the dentist, however, the biocompatibility of a material must be as important as its physical properties [101].