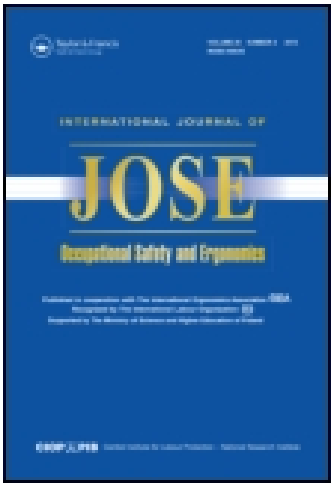

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Evaluating the Potential Occupational Hazard of Handling Dental Polymer Products Using the HET-CAM Technique

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The irritation potencies of 8 dental polymer products, used as dental restorative materials, adhesives, or temporary constructions, were tested using the HET-CAM (hen's egg test-chorioallantoic membrane) technique. Liquid and powder components, and extracts of cured and freshly mixed non-cured materials of 5 glass ionomers, 1 bonding, 1 composite, and 1 cold-cured acrylate were examined. Results showed that the liquid component of all products had a strong irritation capacity but powder suspensions and extracts from cured and freshly mixed non-cured materials had no effect on the CAM. Thus, dental personnel who handle liquid and powder manually are exposed to components with a high irritation potential, in contrast to patients who are exposed to the cured and mixed non-cured materials with low irritation potential. This illustrates the importance of safe handling procedures and practices for dental personnel who handle non-cured polymers manually.

HET-CAM test irritation score dental polymers occupational hazard dental personnel

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1. INTRODUCTION

A variety of polymer products, for example, restorative materials, adhesives, and temporary constructions are used in dentistry. Dental personnel handle non-cured material manually and are therefore at risk. Higher prevalence of dermatitis and eye symptoms are reported by dental personnel compared to controls (Burke, Wilson, & Cheung, 1995; Hensten-Pettersen & Jacobsen, 1991; Hill, Grimwood, Hermesch, & Marks, 1998; Jacobsen, Aasenden, & Hensten-Pettersen, 1991; Jacobsen, Derand, & Hensten-Pettersen, 1996; Jacobsen & Hensten-Pettersen, 1993; Jacobsen & Hensten-Pettersen, 1995; Lönnroth & Shahnavaz 1998a, b, c; Munksgaard, Hansen, Engen, & Holm, 1996; Rustemeyer & Frosh, 1994). Irritant contact dermatitis is the most common type of occupational hand dermatitis (Stingeni, Lapomarda, & Lisi, 1995; Uveges, Grimwood, Slawsky, & Marks, 1995). Patch tests have shown that monomers in dental polymer products can cause allergy (Jolanki, Kanerva, & Estlander, 1995; Jolanki, Kanerva, & Estlander 1996; Kanerva, Estlander, & Jolanki, 1994; Kanerva, Estlander, & Jolanki, 1997; Kanerva, Estlander, Jolanki, & Tarvainen, 1993; Kanerva, Henriks-Eckerman, Jolanki, & Estlander, 1997; Kanerva, Jolanki, & Estlander, 1997; Kanerva, Mikola, Henriks-Eckerman, Jolanki, & Estlander, 1998; Kieć-Świerczyńska 1996; Rustemeyer & Frosch, 1996; Savonius, Keskinen, Tupparainen, & Kanerva, 1993). Once sensitisation is induced, it is self-perpetuating. Occupational skin diseases affect many people and may have serious social and economic consequences for the injured and the society (Halker-Sørensen, 1998).

Basic information on the properties, potential hazards, safe use, and precaution regarding dental restorative materials, is provided in material safety data sheets (MSDS). Different countries have different content requirements but information on known health hazards must be always included. Manufacturers may consider the identity of ingredients to be confidential business information and, in some countries like Canada and the USA, exemptions can apply. However, in Canada a list of ingredients with unknown health hazard is required on MSDSs. In Sweden, a list of content is not required but dental restorative materials, classified as medical technical products, must meet general requirements regarding health and safety for users and patients. A risk-benefit analysis is recommended. The risks must be minimised and, if this is not possible, users must be informed about the risks and precautions (Socialstyrelsen, 1994).

The Draize eye test has been used for more than 40 years to evaluate potential of substances to irritate the eyes and mucous membranes. Following the application of concentrated solutions to the eyes of conscious albino rabbits, irritation reactions such as swelling of the eyelids, inflammation of the iris, ulceration, hemorrhaging (bleeding), and blindness are recorded at specific intervals. The rabbits are immobilised and the eyes are often held open with clips at the lid. However, a growing concern for animal welfare, and the increasing number of chemicals introduced into the market, have emphasised the need for the development of alternative methods to evaluate irritation potential. Several alternatives are being used but, according to de Silva et al. (1997), no universally applicable, validated non-animal alternative is currently available. The Interagency Regulatory Alternatives Group (IRAG) of the USA examined the current scientific status of alternatives to the Draize eye irritation test. Twenty-nine different test methods from 41 laboratories around the world, grouped into five categories (chorioallantoic membrane-based assays, organotypic models, cell function-based assays, cytotoxicity assays, and other systems) were reviewed (Bradlaw, Gupta, Green, Hill, & Wilcox, 1997; Feder, Carr, Holzhutter, Lowell, & Springer, 1997).

According to Spielmann et al. (1997), there are currently two general types of assays based on the chorioallantoic membrane (CAM) in use; the CAMVA (the CAM vascular assay) and the HET-CAM test (hen's egg test-chorioallantoic membrane). In HET-CAM, chemicals are applied to the chorioallantoic membranes of embryonated hen's eggs. Irritation of the chorioallantoic membrane is observed as haemorrhage, lysis, or coagulation, and an irritation score (IS) is calculated. It is assumed that the response of the chorioallantoic membrane reflects the potential for damage to mucous membranes in vivo, in particular, to the eye. According to Spielmann et al. (1993), at least 70% of severely irritant chemicals could be identified correctly using the HET-CAM assay. They suggested a new strategy for eye irritation testing in order to reduce the suffering of rabbits, using HET-CAM in the first stage, and conducting Draize eye tests only for chemicals that scored negative in the HET-CAM test. Also, Wiegleb, Lange, and Kuhnert (1993) emphasised the reduction of animal pain by recommending the use of the HET-CAM test as the first step in distinguishing between irritant and non-irritant substances. Gettings, Lordo, Demetrulis, Feder, and Hintze (1996) reported results from the HET-CAM test to be in

agreement with results from the Draize eye test, but pointed out that the variability associated with the Draize outcome (MAS [maximum average score] value) must be considered, when comparing alternative in vitro methods with the Draize eye irritation test. The reliability and sensitivity of HET-CAM compared to the Draize eye test have been assessed by Mystkowska-Bączkowska, Komar, Samos-Zielińska, Stroińska, and Rogulska (1995). They found HET-CAM to be a rapid, very sensitive method, easy to perform as the chorioallantoic membrane, as complete tissue, includes arteries, capillaries, and veins. They considered the HET-CAM test to be one of the most promising alternative methods of predicting the irritation potential of substances. However, the evaluation is highly subjective and difficult to standardise (Spielmann, 1992).

Lönnroth and Shahnavaz (1998a, b) presented results from an occupational health-based questionnaire study of dental personnel in Northern Sweden. Dental personnel were asked to report symptoms of conjunctivitis, atopic dermatitis, asthma, hay fever/rhinitis, hand dermatitis, and atopy. Further, they were asked to give the names of the various polymer products used and their frequency of use. Results show that dentists reported a higher prevalence of symptoms from skin and eyes than referents and chair assistants. Analysis of the correlation between reported symptoms and the use of a product show that dental personnel with symptoms used eight specific products more frequently than those without symptoms (Lönnroth & Shahnavaz, 1998c).

2. AIM

The aim of this study was to further evaluate the irritation potential of the products that correlated with symptoms in the previous questionnaire study. However, three of the products are no longer available on the market and, in addition, two other commonly used products that had no correlation with the symptoms were chosen.

3. MATERIALS AND METHODS

Dental polymer products for restoration, adhesive, or temporary constructions are supplied either with separate powder and liquid for manual mixing as a paste, or in capsules. The products are cured

chemically, by mixing of two components, or by light. A capsule contains liquid and powder in separate compartments. By activating the capsule, the powder and liquid are brought into contact. The capsule ingredients are then mixed in a high-speed mixer, before insertion into the tooth for polymerisation.

Fuji II was included both as a capsule material and with a separate liquid and powder. Dental personnel, according to Lönnroth and Shahnavaz (1998c) commonly used Fuji II LC and Scotchbond. They were chosen in addition, as their frequent use did not correlate with any symptoms. Only Fuji II LC was tested in the way Scotchbond adhesive and primers were tested in a previous study by Dahl (1999). Data on all tested materials is given in Table 1.

TABLE 1. Data on the Tested Products

Product Name	Manufacturer	Type of Product	Curing	Components	Batch
GROUP I: PRODUCTS WITH ASSOCIATION BETWEEN FREQUENT USE AND SYMPTOMS					
Fuji II	GC Corporation	Glass Ionomer	Light Chemical	Capsule Powder, Liquid	301075 090571, 290971
Ketac Silver	Espe	Glass Ionomer	Light	Capsule	589/067
Lining cement	GC Corporation	Glass Ionomer	Chemical	Powder, Liquid	010761, 280661
Swedon	Svedia	Cold-Cured Acrylate	Chemical	Powder, Liquid	219609, 049510
Super Bond	Sun Medical CO	Bonding	Chemical	Powder, Two Liquids	71105, 70903, 711011
Heliomolar	Vivadent	Composite	Light	Paste	916771
GROUP II: PRODUCTS WITH NO ASSOCIATION BETWEEN FREQUENT USE AND SYMPTOMS					
Fuji LC	GC Corporation	Glass Ionomer	Light	Capsule	091077
Scotchbond*	3M	Primer, Adhesive	Light	Two Liquids	19950125, 19950125

Notes. *—data from Dahl (1999).

HET-CAM tests were performed on each liquid, powder, non-cured, and cured material by preparing powder suspensions and extracts of cured and freshly mixed non-cured materials. Liquids were tested undiluted on the CAM. The liquid and powder were first removed from the capsules of the products supplied in this form. Materials were mixed according to the manufacturer's instructions. The Vivadent Silamat amalgator 2 was used for high speed mixing of capsulated products, for 10 s. Light-cured products were irradiated for 40 s using a 3M XL300 curing lamp (3M Company). All extracts and suspensions were prepared at 37 °C under agitation for 24 hrs according to ISO 10993-12 (International Organization for Standardization [ISO], 1996).

3.1. Suspensions of Powders

A 10% powder suspension was prepared by mixing the powder with a cell culture medium (MEM + 2 mM L-glutamine + 100 IU/ml penicillin + 100 mg/ml streptomycin + 5% FBS) in tubes. The cell culture medium was used to prepare all suspensions and extracts for this test, as this also provides suitable materials for testing on cell cultures (results not presented here). The tubes were incubated for 24 hrs in a water bath at 37 °C, under agitation. The suspensions were then centrifuged and the supernatants applied to the CAM.

3.2. Extracts of Freshly Mixed Non-Cured Materials

These extracts were prepared according to ISO 10993-12 (ISO, 1996): 0.1 g/ml medium for samples with an irregular surface area. Freshly mixed materials were placed into foil-covered tubes (to protect the materials from light), weighed and the appropriate amount of medium was added. The tubes were incubated for 24 hrs in a water bath at 37 °C, under agitation. The extracts were pipetted into fresh tubes and then applied to the CAM.

3.3. Extracts of Cured Materials

These extracts were prepared according to ISO 10993-12 (ISO, 1996): 1.25 cm^2 sample surface area/ml of medium. The polymerised products

were cured in cylindrical Teflon moulds, giving a sample diameter of 4 mm and a height of 6 mm. The samples and medium were placed in glass vials and incubated for 6 days in a water bath at 37 °C, under agitation, then left for 24 hrs to let particles settle. The extracts were then filtered using Millex-GS (0.22 μm) sterile filters prior to application to the CAM. The extracts were filtered in order to remove finer particulate matter, the presence of which might interfere in the assessment of the effects of extracts on the HET-CAM test.

3.4. Test Procedure

The HET-CAM procedure was slightly modified from Kalweit, Besoke, Gerner, and Spielmann (1990). Embryonated hen's eggs were delivered 8 days old, from the National Institute of Public Health, Oslo, Norway. The eggs were incubated at 38 °C until testing on day 9. The shell membrane above the air cell was opened using a dental drill saw blade and forceps. The shell membrane was moistened with 0.9% NaCl solution at 37 °C. The NaCl was aspirated, the shell membrane carefully removed, and the CAM exposed. The eggs were examined using a microscope (Wild Photomakroskop M400, Heerbrugg, Switzerland). Photomicrographs were taken 2 min after the application of each material.

Test solutions and controls were equilibrated to 37 °C prior to application. As positive control 0.1 N NaOH was used, and as negative control 0.9% NaCl. The test solutions were applied to the CAM in a volume of 0.1–0.2 ml. All tests were performed without the observer knowing which extract was used. The arteries, capillaries, and veins where examined for irritant effects such as haemorrhage, lysis, and coagulation. Observations were made prior to application, after 30 s, 1, 2, 3, and 4 min. The irritation score was calculated for each egg according to Spielmann (1992), using the formula

$$\frac{(301 - \mathrm{sH})}{300} \times 5 + \frac{(301 - \mathrm{sL})}{300} \times 7 + \frac{(301 - \mathrm{sC})}{300} \times 9 = \text{Score for each egg}$$

where H—haemorrhage, L—lysis, C—coagulation, s—reaction time from the start of exposure to the occurrence of effects.

One experiment included 6 eggs. Each material was tested on 3 eggs, and the test was repeated once. The average score (based on 6 eggs) was

calculated for each material, and test materials were classified as non-irritant (0.0–0.9), slightly irritant (1.0–4.9), moderately irritant (5.0–8.9), and strongly irritant (score 9.0–21.0).

Additionally, to evaluate the variability of results for each reaction, the mean value and *SD* (standard deviation) were also calculated for each reaction according to

$$\mathrm{H} = \frac{(301 - \text{s for H})}{300} \times 5,\ \mathrm{L} = \frac{(301 - \text{s for L})}{300} \times 7,\ \mathrm{C} = \frac{(301 - \text{s for C})}{300} \times 9.$$

For reactions with a higher *SD* than the mean value, the experiment (with the same extract) was repeated. This was done for six samples.

4. RESULTS

The calculated irritation scores are given in Table 2. For repeated tests, the irritation scores presented in the table are from the second series.

The main constituent of the glass ionomers (Fuji II, Fuji II cap, Ketac Silver, Lining cement, and Fuji LC) is an odourless liquid based on polyacrylic acid. Fuji II LC also contains 2-HEMA (2-hydroxyethyl dimethacrylate). The undiluted liquids of all the glass ionomers had strong effects on the CAM. The first effect, coagulation of blood vessels, came after 30 to 60 s. Then (in 30 to 120 s), blood vessels "disappeared" due to the effect of lysis.

When applying the strongly smelling undiluted liquids of Swedon and Super-Bond on the CAM, the first effect observed was bleeding from the blood vessels within 30 s, followed almost immediately by coagulation of blood vessels and lysis. The main constituent of Swedon and Super-Bond is MMA (methyl methacrylate). To provide excellent bonding property Super-Bond also contains a derivative of MMA, 4-Meta (4-methacryloxyethyl trimellitate anhydride). Similar effects, but slower (which is shown by a slightly lower IS score) was seen after applying the odourless Scotchbond primer or adhesive on the CAM. The main constituents in these liquids are 2-HEMA (2-hydroxyethyl methacrylate) and BIS-GMA (Bisphenol A diglycidyl dimethacrylate). None of the extracts of freshly mixed non-cured or cured materials gave any effect on the CAM (Table 2). This indicates that the irritation potential for the patients is low.

TABLE 2. Irritant Score For Non-Diluted Liquids, Powder Suspensions, Extracts of Freshly-Mixed Non-Cured Products, and Extracts From Cured Products, as Calculated From the 6 Eggs Tested

Product Name	Non-Irritant	Slightly Irritant	Moderately Irritant	Strongly Irritant	First Effect	Later Effects
Liquids						
Fuji II cap				13.3	Coagulation, Lysis	Lysis
Fuji II				12.5	Coagulation	Haemorrhage, Lysis
Ketac Silver cap				12.9	Coagulation, Lysis	
Lining cement				12.6	Coagulation, Lysis	
Swedon				19.0	Haemorrhage, Coagulation, Lysis,	
Super Bond, monomer				16.9	Haemorrhage, Coagulation	Lysis
Super Bond, catalyse				12.6	Haemorrhage, Coagulation	
Fuji LC cap				11.8	Coagulation	Lysis
Scotchbond primer				9.9*	Haemorrhage	Coagulation
Scotchbond adhesive			6.3*		Haemorrhage	Coagulation
Powder suspension						
Fuji II cap	0.0					
Fuji II	0.0					
Ketac Silver cap	0.0					
Lining cement	0.0					
Swedon	0.0					
Super Bond	0.5				Coagulation, Lysis	
Fuji LC cap	0.0					
Extracts of freshly mixed non-cured products						
Fuji II cap	0.0					
Fuji II	0.0					
Ketac Silver cap	0.0					
Lining cement	0.0					
Swedon	0.0					
Super Bond	0.0					
Heliomolar	0.0					
Fuji LC cap	0.0					
Extracts of cured products						
Fuji II cap	0.0					
Fuji II	0.0					
Ketac Silver cap	0.0					
Lining cement	0.0					
Swedon	0.0					
Super Bond	0.0					
Heliomolar	0.0					
Fuji LC cap	0.0					

Notes. *—data from Dahl (1999).

When calculating mean time for each effect, it was shown that mainly the time of lysis varied considerably between the six tests (*SD* higher than the mean value) for six materials. After repeating the tests with the same liquids and powder suspensions but focusing more on the lysis effect the difference decreased as shown in Table 3.

According to Table 3, the first tests with powder suspensions of Lining cement and Super-Bond gave slight effects on the CAM. When repeating the tests on another 6 eggs, there was no consistency in the result regarding Super-Bond suspension as effect was seen only on a single egg. Further, it was not possible to determine whether the effect was due to the chemical content of the material or mechanical damage when applying the powder suspension on the blood vessels.

5. DISCUSSION

The HET-CAM test is considered by Spielmann et al. (1993) to be a valid method for identifying severely irritant substances but not useful for safety assessment of slightly irritant substances. A comprehensive scheme for scoring, use of a positive control, and blind testing were used to reduce the subjective aspect of the assessments. Further, results were

TABLE 3. Mean Value and *SD* for Each Reaction, and For Initial and Repeated Tests

	Haemorrhage		Lysis		Coagulation	
Product Name	Initial Mean (*SD*)	Repeated Mean (*SD*)	Initial Mean (*SD*)	Repeated Mean (*SD*)	Initial Mean (*SD*)	Repeated Mean (*SD*)
Liquids						
Ketac Silver cap	0 (0)	0 (0)	2.3 (2.6)	5.6 (0)	6.6 (0.9)	7.2 (0)
Super Bond, catalyst	1.0 (1.7)	4.5 (0)	1.4 (2.2)	0 (0)	7.4 (1.2)	8.1 (0)
Super Bond monomer	4.0 (1.0)	4.5 (0)	2.8 (3.1)	4.2 (0)	7.4 (1.1)	8.1 (0)
Fuji LC cap	0 (0)	0 (0)	2.8 (3.1)	4.7 (0.7)	7.2 (0)	7.4 (0.4)
Powders						
Lining cement	0.7 (1.7)	0 (0)	2.1 (2.3)	0 (0)	3.9 (3.7)	0 (0)
Super Bond	0 (0)	0 (0)	2.1 (2.3)	0.2 (0.6)	6.3 (3.3)	0.3 (0.7)

analysed with respect to each type of effect: haemorrhage, lysis, and coagulation, and the mean and *SD* were calculated. The time for the onset of lysis varied considerably between the individual tests for six of the materials. This might be explained by the fact that it is more difficult to assess the disappearance of the small blood vessels in a lysis effect, than haemorrhage and coagulation. When repeating the tests, concentrating more on the observation of lysis, the variability decreased. This indicates that, in addition to the IS score, it might be useful to also calculate the mean and *SD* for each effect. This is in agreement with Kalweit et al. (1990), who reported that results obtained by less experienced and less well trained investigators differ considerably.

Glass ionomers were considered quite harmless by dental personnel, and Swedon and Super-Bond the most hazardous materials to handle (Lönnroth & Shahnavaz, 1998a). However, all undiluted liquid components of the tested products were shown to be strongly irritating. After repeating six tests, the evidence was even stronger. Powder suspensions of Lining cement and Super Bond were shown to be slightly irritant (IS 4.3 vs. 6.5) in the first test series. However, on repeating the tests, only Super Bond powder suspension caused any effect (IS 0.5) to the CAM. It was not possible to distinguish effects due to mechanical damage to the vessels, from irritation effects, after applying the powder suspension to the CAM. This illustrates the limitation of the HET-CAM method in evaluating chemicals that are not strong irritants.

From the material safety data sheets on the products, it was not possible to identify a common component that could be responsible for the effects, as information on composition was far from comprehensive. According to material safety data sheets on Fuji and Lining cement, both powders and liquids may irritate due to low pH. Results from this study showed the liquids to be strongly irritating and the powder non-irritant. Information provided on one glass ionomer in this study, Ketac Silver, classified the liquid as non-irritant, contradictory to our results showing it to be strongly irritating.

Dahl (1999) and Schendel, Erdinger, Komposch, and Sonntag (1994, 1995) earlier used the HET-CAM method for testing adhesives and bonding materials. They found that the effect on HET-CAM varied considerably with similar products, but they could not find a clear correlation between the content of the product and the effect. However, material safety data sheets are far from comprehensive and need to be improved, as also pointed out by Kanerva, Henriks-Eckerman, et al. (1997).

A primary irritant has the capability of causing damage in everyone

if it is present in sufficient concentration for a sufficiently long time, as pointed out by Hensten-Pettersen (1998). Also, repeated contacts to low doses of irritants over extended periods of time can damage skin or mucosal barriers and thus enhance entry of allergens.

Dental personnel are exposed to a number of occupational hazards. The occupational health hazards when handling amalgam are inhalation of mercury vapour and skin contact to mercury. Even though studies have documented a higher level of mercury in blood, urine, faeces, and accumulated in the brain and kidneys in dental personnel, the effect of this is still under debate. Single cases have been reported of poisoned dental personnel accidentally exposed to a high level of mercury. Allergy to mercury is rare, even among dental personnel where it has been used for more than 100 years. Universal handling practices and procedures are available on amalgam but not on polymer products. Polymer products were first introduced about 50 years ago. Today they are essential in dental practices due to high aesthetic and adhesion properties. In contrast to industrial use, dental use requires manual handling of monomer containing products. The occupational health hazards with dental polymer products is mainly dermatitis and allergy. Monomers in polymer products can easily penetrate all kind of gloves used in dentistry (Munksgaard, 1992). Further, once sensitised, the consequence is serious for the dentist or chair assistant who might have to leave the profession. Dermal effect is the second most common work-related disease in dentistry (after musculoskeletal symptoms) and the problem is increasing (Jacobsen & Hensten-Pettersen, 1993).

This study indicates that products associated with certain clinical symptoms of irritation in dental personnel are strongly irritating. However, products commonly used, without association to symptoms, also have strong irritation potency. Some of the clinical symptoms may be related to volatile components, which the HET-CAM test is not designed for. None of the extracts from cured or freshly-mixed non-cured products, gave an effect in HET-CAM tests, indicating a lower irritation potency for the mixed products but, to prove that the irritation potential is zero, further studies, including the Draize eye test, are required. This study indicates that patients are exposed to materials with lower irritation potency than dental personnel, who handle the non-cured products manually. This highlights the importance of learning how to handle all dental polymers, especially the liquids, in a safe manner. Further, material safety data sheets need to be improved, giving all necessary information regarding hazards and precautions.

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