

## Preservation of products with MCI/MI in Switzerland

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Preservation of products with the combination of 5-chloro-2-methyl-4-isothiazolinone (methylchloroisothiazolinone, MCI) and 2-methyl-4-isothiazolinone (methylisothiazolinone, MI), commercialized as Kathon CG or WT, is widely used. Allergic contact dermatitis reactions to the preservative have been described in many publications of epidemiological studies. In addition, a number of allergic, airborne reactions to MCI/MI were observed in recent years. The aim of the presented study was: (i) to compare epidemiological data of MCI/MI with data of other preservatives; (ii) to estimate the possible exposure to MCI/MI from commercial products and the distribution of MCI/MI in chemical products based on a product evaluation of the chemical product register of the Swiss Federal Office of Public Health; (iii) to estimate the exposure to MCI/MI, volatile organic chemicals (VOC) and glycols from freshly painted walls; (iv) to compare the contact allergenic potential of MCI/MI with other preservatives. It was found that the number of registered chemical products, unambiguously identifiable as containing MCI increased from 3644 products in July 1999 to 4843 products in April 2001 in Switzerland. It is estimated that today, the total number of chemical products preserved with MCI/MI on the Swiss market is about 6000. A further increase is to be expected. The contact allergenic potential of MCI/MI seems to be higher than for other preservatives. Measurements of MCI/MI concentrations in air samples of freshly painted rooms have shown that the concentration of MCI/MI in the air a few days after painting may be high enough to elicit airborne reactions in already-sensitized patients. In a single case, reactions to MCI/MI were observed over months after wall painting. In this case, both wall paint and plaster contained MCI (40 and 46 ppm). Volatile organic chemicals (VOC) may also be relevant for the elicitation of airborne reactions. In  $\frac{1}{3}$  of the measurements, the VOC concentrations measured within 14 days after painting were in a range within which sensory irritation and discomfort may be induced. Declaration of MCI/MI-containing products, replacement of MCI/MI by alternative preservatives or the separate use of preservatives in industrial products and in cosmetics might reduce the risk of airborne reactions.

**Key words:** MCI/MI; Kathon; preservatives; industrial products; distribution; airborne reactions; volatile organic chemicals; VOC; glycols. © Munksgaard, 2001.

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The combination of 5-chloro-2-methyl-4-isothiazolinone (methylchloroisothiazolinone, MCI) and 2-methyl-4-isothiazolinone (methylisothiazolinone, MI), generally used in a proportion of 3:1, is used as preservative in various areas, including cosmetics and hygiene products, cooling and cutting oils, emulsions, paints, paper, wood protection agents, plant protection products etc. (1). MCI/MI was primarily used in cosmetics. Allergic reactions due to MCI/MI in cosmetics were described in many epidemiological studies. The replacement of solvent-based paints by water-based paints in the

last decade led to the necessity to preserve the more ecological, water-based paints. MCI/MI became the most commonly used preservative in water-based paints. In recent years several cases with airborne reactions to MCI/MI due to exposure to MCI/MI from freshly painted walls were described.

We reviewed the published literature to get an impression of the epidemiological data on allergic reactions to MCI/MI and to alternative preservatives. We reviewed the product registry of the Swiss Federal Office of Public Health (FOPH) to get an estimate

of the distribution of MCI/MI in industrial products. To clarify the exposure situation in freshly painted rooms, measurements of important components of water-based paints (MCI/MI, volatile organic chemical, glycols) were performed.

### Materials and Methods

#### *Product registry*

For more than 25 years, Switzerland has had chemical product registers which today includes over 130,000 records. According to the Swiss toxic substance law, registration of chemical substances and products for public or commercial use is a prerequisite for placing the substance or product on the market. The registered substances and products are published periodically in 3 so-called "toxic substance lists". The 2 product registers (toxic list 2, products for public use, and 3, products for commercial use) include the brand name of the product, the toxic substance class (Swiss classification system), followed by some remarks, the intended use of the product and the name of the registrant. List 2 has about 33,000, List 3 about 97,000 records. The source data base at the Chemical Products Division of the Swiss Federal Office of Public Health has much more information, which, due to the confidentiality of the data, is not published. The data include, among other items, the full composition of the product, the name of the manufacturer and the purpose and type of application. Due to confidentiality, in many cases, the chemical products division of FOPH receives the full composition not from the registrant in Switzerland, but directly from the (foreign) manufacturer. The register plays an important rôle for the trade with chemicals and preparations (published lists), but also for market control and prevention measures. In risk assessment, the source database at FOPH is of great value, since exposures of the public to dangerous or otherwise problematic substances from chemical products can be identified and characterized. In this study, we used the data

to discuss exposures to MCI/MI from chemical products in the indoor environment.

#### *Indoor air measurements*

The 1st sample in each room was collected within 14 days after painting; later samples were collected during weeks 2 to 13 after painting.

#### *MCI/MI*

Air samples were collected in 42 freshly painted rooms in the area of Zürich and Basel. The collection was made over a time period of 4 to 16 h; the air flow was 300 to 400 ml/min. MCI/MI was absorbed in a solution with 1% formic acid and was quantified gas chromatographically (GC-NPD/ECD), as described in Niederer (2). The absolute threshold of detection was 2 pg MCI/MI; the lowest detectable air concentration with a sampling time of 16 hours was 0.01  $\mu\text{g}/\text{m}^3$ .

#### *Volatile organic chemicals (VOC)*

19 rooms in different buildings were selected to measure VOC at 2 time-points after painting. Selection criterion was the use of water-based wall paint containing glycols and the preservative MCI/MI. The samples were analysed for typical indoor VOC like alkanes, aromatics, terpenes, aldehydes, esters of alcohols and glycols.

#### *Review of use and epidemiology of allergic reactions to MCI/MI*

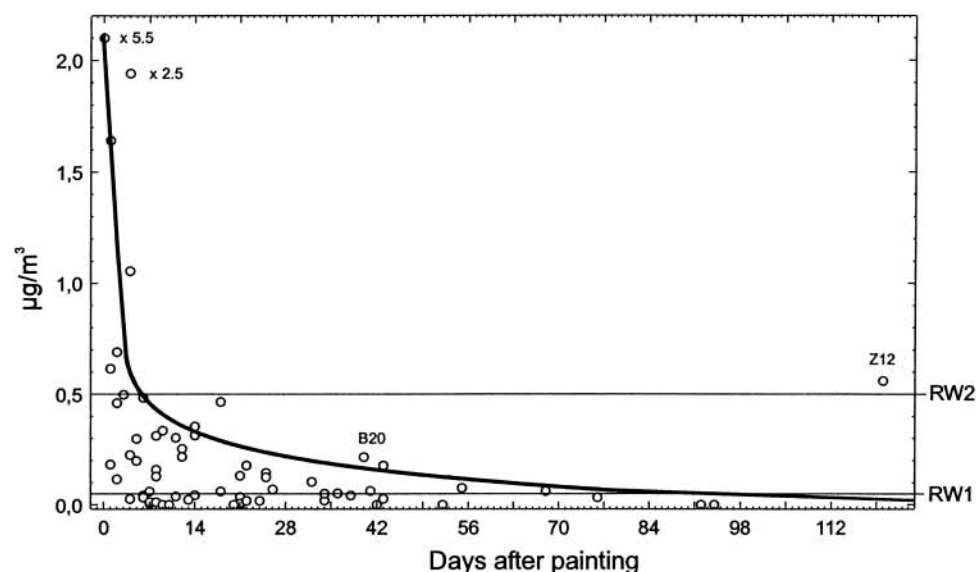
The combination of MCI/MI is used as preservative in cosmetics and in chemical products, in household products as well as in industrial products, such as cooling oils, paints, cleaning solutions and formulations of biocides (1, 3).

A multicentre study in Europe shows well the incidence and variations of allergic reactions to MCI/MI in various European countries and the

Table 1. Epidemiology of contact dermatitis from MCI/MI

| Years of examination | Country     | No. of patients tested | % of positive reactions |       | Ref. |
|----------------------|-------------|------------------------|-------------------------|-------|------|
| 1990–1994            | Germany     | 27,331                 | 2.6%                    |       | (5)  |
| 1990–1994            | Switzerland | 5565                   | 1990                    | 3.2%  | (6)  |
|                      |             |                        | 1992                    | 3.9%  |      |
|                      |             |                        | 1994                    | 1.8%  |      |
| 1985–1997            | Belgium     | 8521                   | 1.5%                    |       | (7)  |
| 1992–1996            | USA         | 3507                   | 1992–94                 | 2.9%  | (8)  |
|                      |             | 3075                   | 1994–96                 | 3.0%  |      |
| 1989–1992            | Japan       | 493                    | 1989                    | 1.2%  | (9)  |
|                      |             | 830                    | 1991                    | 0.6%  |      |
|                      |             | 975                    | 1992                    | 0.82% |      |

Fig. 1. Indoor air concentrations of the preservative 5-chloro-2-methyl-4-isothiazolinone (MCI) in 42 rooms as a function of time (days).



dependence on patient selections (4). The % of positive reactions to MCI/MI varied in different European countries from 0.4% to 11.1% (4). A summary of some recent publications is given in Table 1.

A clear reduction in the % of positive reactions in tested patients is seen in Switzerland in 1994 compared to 1990 (6), whereas the incidence in Germany and the USA was still higher than 2%. In Japan, where MCI/MI is accepted (15 ppm) in rinse-off products only, the incidence was clearly lower (9); in The Netherlands, the incidence of reactions to rinse-off products was higher (3.2%) in 1994 (9).

In the industrial environment, MCI/MI is used in higher concentrations than in cosmetics. It is on the market as a concentrated solution (1.5–13.5%) and it is recommended that it be diluted to concentrations of 15–55 ppm. Therefore, the exposure to MCI/MI in the industrial environment may currently be higher than the exposure due to cosmetics. New regulations on the use of MCI/MI in industrial products are ongoing in the EU.

The cause for the induction of sensitization to MCI/MI is in most cases exposure to cosmetics; e.g., from 202 tested employees, 5 reacted to MCI/MI in paints, only 3 of these being related to exposure in industry (10). In another study, 22 out of 626 tested persons reacted to MCI/MI, but not a single case could be clearly related to industrial work (11). The importance of cosmetics as a primary cause of sensitization to MCI/MI is also supported by the epidemiological studies of Goossens et al. (7, 12). When consecutive patients were tested in dermatology clinics, the prevalence of positive reactions to MCI/MI was 1.5% (7). When 475 se-

lected patients with suspected allergy to cosmetics were tested, the frequency of allergic reactions to MCI/MI increased to 9.9% (12).

Reactions of the skin and the mucous membranes after moving into new or renovated rooms may be due to various factors, such as non-specific irritant reactions to formaldehyde and volatile organic chemicals (VOC) or to specific allergens. A good diagnostic evaluation of the reactions by a dermatologist or allergologist in collaboration with an environmental hygiene laboratory is needed. Specific airborne reactions to MCI/MI were described in the literature and, with 1 exception, were all related to exposure to paints. Individual cases were described by Finkbeiner & Kleinhans (13), Fernandez et al. (14), Schubert (15) and Bentrop et al. (16); groups of patients were described by Hausen (1) and Bohn et al. (17). Reactions were observed within a few days after wall painting on the face, neck, forearms, hands, lower legs and chest. In addition, conjunctival irritation and cough may occur, and hospitalization may be needed in severe cases (1, 17).

## Results and Discussion

### *Exposure to MCI/MI and volatile organic compounds (VOC) in freshly painted rooms*

Measurements in 42 freshly-painted rooms showed that the concentration of MCI in the air decreases to approx. 25% of the initial concentrations within 7 days (Fig. 1) (2). During the 2nd week after painting, all samples, except 1, decreased below 0.5 µg/m<sup>3</sup>; a concentration which was reported to elicit airborne reactions in sensitive patients (1). In 1 case, the concentration was higher than 0.5 µg/m<sup>3</sup>

Table 2. Concentrations of volatile organic compounds and of MCI in the air of freshly painted rooms (19 buildings, early and late measurements)

|                                             | Early measurements (n=19)               |        |               | Late measurements (n=19)                |        |               |
|---------------------------------------------|-----------------------------------------|--------|---------------|-----------------------------------------|--------|---------------|
|                                             | mean (SD)                               | median | maximum value | mean (SD)                               | median | maximum value |
| Days after painting                         | 6.5 (4.1)                               | 5      | 14            | 45.8 (24.4)                             | 38     | 94            |
| VOC concentrations $\mu\text{g}/\text{m}^3$ |                                         |        |               |                                         |        |               |
| alkanes                                     | 1122 (2825)                             | 192    | 12,548        | 247 (426)                               | 130    | 1938          |
| alkenes                                     | 32 (71)                                 | 0      | 230           | 10 (11)                                 | 5      | 30            |
| aromatics                                   | 723 (1304)                              | 233    | 5703          | 133 (142)                               | 80     | 595           |
| alcohols                                    | 282 (517)                               | 105    | 2311          | 256 (265)                               | 162    | 876           |
| esters                                      | 714 (1509)                              | 138    | 5392          | 250 (620)                               | 19     | 2060          |
| glycols and their derivatives               | 1575 (1364)                             | 1099   | 4073          | 373 (293)                               | 274    | 1209          |
| aldehydes (C4-C10)                          | 164 (290)                               | 37     | 1216          | 49 (35)                                 | 49     | 151           |
| ketones                                     | 59 (59)                                 | 31     | 180           | 33 (49)                                 | 12     | 175           |
| terpenes                                    | 42 (45)                                 | 28     | 194           | 30 (19)                                 | 24     | 66            |
| halogenated cpds                            | 5 (6)                                   | 3      | 20            | 2 (3)                                   | 1      | 11            |
| others                                      | 81 (154)                                | 22     | 466           | 18 (16)                                 | 10     | 54            |
| TVOC<br>(sum of identified compounds)       | 4799 (5449)                             | 3229   | 17,876        | 1403 (1066)                             | 1026   | 3777          |
| MCI                                         | 0.56 <sup>a)</sup> (1.12) <sup>a)</sup> | 0.2    | 4.85          | 0.06 <sup>a)</sup> (0.11) <sup>a)</sup> | 0.03   | 0.47          |

<sup>a)</sup> values below the detection limit ( $0.01 \mu\text{g}/\text{m}^3$ ) were set to  $0.005 \mu\text{g}/\text{m}^3$  for calculation.

Table 3. Tentative dose-response relationship for discomfort resulting from exposure to solvent-like volatile organic compounds as air pollutants in non-industrial indoor environments (20)

| Total VOC concentration $\text{mg}/\text{m}^3$ | Irritation and discomfort                                                 | Exposure range                    |
|------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------|
| <0.20                                          | no irritation or discomfort                                               | comfort range                     |
| 0.20–3.0                                       | irritation and discomfort possible if other exposures interact            | range of multifactorial exposures |
| 3.0–25                                         | exposure effects and probable headache possible if other factors interact | range of discomfort               |
| >25                                            | headache                                                                  | toxic exposure range              |
|                                                | additional neurotoxic effects other than headache may occur               |                                   |

over a period of more than 120 days; point Z12. This was an actual case with airborne contact dermatitis to MCI. Based on measurements in various types of rooms, a concentration of  $1\text{--}5 \mu\text{g}/\text{m}^3$  was classified as tolerable in another publication (citation in (1)). This may be the case for people not already sensitized to MCI/MI, but not for sensitized persons.

The threshold values shown, RW1 and RW2, were selected from the MAK-value of 1998 for MCI of  $50 \mu\text{g}/\text{m}^3$ , factor 100 and 1000 of MAK. The concentration of MCI/MI in the air is dependent on various factors, such as time after painting, type of paint or plaster and its time of storage, loading factor (painted area per volume), air change rate, etc. Comparisons of various paints have shown that, even within 1 producer, the concentration of MCI/MI may vary from batch to batch (2). In the problem case with high indoor air concentrations, it was found that both wall paint and plaster contained MCI. The measured product concentrations were 40 ppm and 46 ppm, respectively.

Comparable indoor exposure levels were measured by 2 groups in Germany. Measurements in 2

office rooms showed concentrations of  $5\text{--}31 \mu\text{g}/\text{m}^3$  1 day after painting and  $2\text{--}6 \mu\text{g}/\text{m}^3$  7 days after painting (18). The disinfection of water in ventilation systems (humidifiers, cooling towers) lead to MCI concentrations in the mechanically ventilated rooms of up to  $3 \mu\text{g}/\text{m}^3$  (19).

As shown in Table 2, the VOC concentrations showed a high variation in the 19 measured rooms; the difference between the minimal and maximal values lies in the range of factor 100. The 1st sample in each room was collected within 14 days after painting; later samples were collected during weeks 2 to 13 after painting. Selection was according to the use of water-based paints containing glycols (or derivatives) and the preservative MCI.

Møhlave (20) and other researchers exposed volunteers to different concentrations of a mixture of 22 VOC typically occurring in Danish buildings in the early 80s. Based on the results of these controlled exposure experiments and of field studies, Møhlave (20) proposed a dose-response relationship for low-level exposures to VOC.

According to the proposal of Møhlave,  $1/3$  of the measured VOC concentrations in the first 14 days after painting were in the range of discomfort. In

Table 4. Distribution of MCI (from MCI/MI) in chemical products in Switzerland in 1999

| Product group                          | No. chemical products | %    |
|----------------------------------------|-----------------------|------|
| paints, varnishes, coatings            | 1393                  | 38.2 |
| adhesives, sealants, plasters, fillers | 594                   | 16.3 |
| cleaning products                      | 536                   | 14.7 |
| auxiliary compounds                    | 419                   | 11.5 |
| washing powders                        | 47                    | 1.3  |
| dishwashing agents                     | 48                    | 1.3  |
| fungicides                             | 78                    | 2.1  |
| floor care products                    | 86                    | 2.4  |
| car care products                      | 63                    | 1.8  |
| remaining products                     | 380                   | 10.4 |
| total no. of identified products       | 3644                  | 100  |

the last 10 years, there was a reduction of high exposures to solvent-like VOC due to the change to water-based paints, adhesives and other building products. In Switzerland, Rothweiler et al. (21) measured VOC in 22 new and renovated buildings in 1989–1991. They reported TVOC concentrations up to 35.6 mg/m<sup>3</sup>, with a median value of 9.5 mg/m<sup>3</sup>. On the other hand, however, the changes in building products produced a shift to more polar compounds and unsaturated hydrocarbons in indoor air; glycols and their derivatives (Table 2), terpenes, higher aldehydes and ketones becoming more and more important. Several of these compounds (e.g., C<sub>6</sub>–C<sub>10</sub> aldehydes, 2-butoxyethanol) exhibit very low-odor thresholds and may lead to complaints of sensory irritation and headaches (22–24). Moreover, unsaturated compounds in air (e.g., terpenes) or on surfaces (e.g., fatty acids) can readily react with ozone and strong irritants may be formed (25, 26).

### MCI/MI in industrial products

A survey in July 1999 has shown that MCI/MI was included in at least 3644 chemical products in Switzerland (cosmetics are not included). However, the real number of products containing MCI on the Swiss market is greater, since in a number of datasets in the Swiss product register, collective terms for preservatives like “preservative” and “isothiazolone salt” were used. From the data, it is estimated that an additional 1200–1500 chemical products contain MCI. Table 4 shows the distribution of identified products containing MCI in the main product groups.

Table 4 shows the importance of MCI/MI as a preservative of paints and other products often used in buildings. Of all the products that could be identified containing MCI, nearly 40% belong to the product class of paints. From the data in the product register, it can be estimated that more than 1/3 of all water-based paints (including paints, varnishes, coatings) contain MCI. In a review of 523 products in Denmark 1993, 169 paints (32%) were preserved with MCI/MI (27). However, if only typical water-based wall paints for indoor use are concerned, the proportion of products containing MCI would rise up to 80% or more: in summer 2000, a consumer protection magazine sampled 16 water-based wall paints available on the Swiss market; the analysis (Kantonales Laboratorium Basel-Stadt) showed that all products contained MCI (28). The number of chemical products preserved with MCI/MI in the Swiss product register is sharply increasing, from 3644 in July 1999 to 4161 in July 2000 and to 4843 in April 2001. Together with the datasets from products, where the

Table 5. Number of products preserved with various preservatives as of July 2000

| Product group/preservative             | No. chemical products | Total no. and % |
|----------------------------------------|-----------------------|-----------------|
| Paints, varnishes, coatings            |                       |                 |
| MCI <sup>a)</sup> (MCI/MI)             | 1393                  | 42.9%           |
| BIT <sup>a)</sup>                      | 616                   | 19.1%           |
| chloroacetamide                        | 321                   | 9.9%            |
| chloro-N-(hydroxymethyl)acetamide      | 449                   | 13.8%           |
| octhilinone                            | 262                   | 8.1%            |
| benzylhemiformal                       | 40                    | 1.2%            |
| BHT <sup>a)</sup>                      | 163                   | 5.0%            |
| total <sup>b)</sup>                    | 3244                  | 100%            |
| Adhesives, sealants, plasters, fillers |                       |                 |
| MCI <sup>a)</sup> (MCI/MI)             | 594                   | 45.0%           |
| BIT <sup>a)</sup>                      | 329                   | 24.9%           |
| chloroacetamide                        | 104                   | 7.9%            |
| BHT <sup>a)</sup>                      | 189                   | 14.3%           |
| octhilinone                            | 19                    | 1.5%            |
| chloro-N-(hydroxymethyl)acetamide      | 85                    | 6.4%            |
| total <sup>b)</sup>                    | 1320                  | 100%            |

<sup>a)</sup> MCI: 5-chloro-2-methyl-4-isothiazolin-3-one; BIT: benzisothiazolinon; BHT: butylated hydroxytoluene.

<sup>b)</sup> Number of products containing frequently used preservatives.

Table 6. Results of predictive tests with chemicals of Table 5

| Chemical             | Method       | Induction-concentration | Results               | Ref.    |
|----------------------|--------------|-------------------------|-----------------------|---------|
| MCI/MI <sup>a)</sup> | Bühler       | 0.2%                    | 20/20                 | (in 29) |
|                      |              | 0.05%                   | 10/10                 |         |
|                      |              | 0.01%                   | 9/15                  |         |
|                      |              | 3 ppm                   | 5/5                   |         |
|                      |              | 30 ppm                  | 5/5                   |         |
|                      | maximization | 100 ppm                 | 4/5                   | (31)    |
|                      |              | 3%                      | PI <sup>b)</sup> 16.7 |         |
|                      |              | 0.3%                    | PI 28.1               |         |
|                      |              | 0.03%                   | PI 12.3               |         |
|                      |              | 0.003%                  | PI 0.9                |         |
| BIT <sup>a)</sup>    | LLNA         | 1000 ppm                | PI 48.2               | (32)    |
|                      |              | 500 ppm                 | PI 27.8               |         |
|                      |              | 50 ppm                  | PI 8.1                |         |
|                      |              | 5%                      | 3/20                  |         |
|                      |              | 50%                     | PI 4.97               |         |
|                      | maximization | 30%                     | PI 4.45               | (32)    |
|                      |              | 10%                     | PI 3.84               |         |
|                      |              | 3%                      | PI 2.72               |         |
|                      |              | 0.003%                  | 3–5/5                 |         |
|                      |              | 0.03%                   | 3–5/5                 |         |
| chloroacetamide      | maximization | 0.3%                    | 1–5/5                 | (34)    |
|                      |              |                         |                       |         |
|                      |              |                         |                       |         |

<sup>a)</sup> MCI/MI: 5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one (Kathon CG); BIT: benzisothiazolinone.

<sup>b)</sup> PI: proliferation index (significant PI: 3 and higher).

exact preservative could not be identified, it is estimated that today more than 6000 chemical products on the Swiss market contain MCI.

In Table 5, the number of paints and adhesives preserved with MCI/MI is compared with other preservatives. The comparison with other preservatives demonstrates again the importance of MCI/MI in paints and adhesives. Benzisothiazolinone (BIT) is the 2nd most used preservative in these product groups.

#### Comparison of predictive testing methods

For more than 50 years predictive animal methods have been performed. Various guinea pig test

methods were developed and were adapted to 2 special aims.

*To obtain a high sensitivity of prediction and the possibility of obtaining positive results also with moderate and weak allergens.* The primary factor in achieving such an increase in sensitivity was the introduction of Freund's complete adjuvant injections during the induction phase, as in the FCA test, the optimization test, the split adjuvant test or the maximization test (29, 30).

*To mimic the exposure situation in man by using topical exposure also in the guinea pig.* Open applications are used in the OET (open epidermal test) and occlusive treatments are used in the Bühler test (29, 30).

Characteristic of all guinea pig methods are that the normal test includes 3 main phases (induction phase, rest period and challenge or provocation phase) and that a compound was classified as sensitizer or not according to the number of reactions observed in the challenge phase.

With the revision of the OECD guideline in 1987, the number of recommended guinea pig tests was reduced to the most frequently-used tests, the maximization test and the Bühler test.

In recent years, the mouse local lymph node assay (LLNA) has gained in importance (30). This test is limited to an induction phase and the compound is classified as sensitizer according to the primary induction of proliferation of the local lymph node by measuring the incorporation of radioactive thymidine. Compounds inducing a proliferation index of higher than 3, compared to the vehicle control, are classified as sensitizers. By using several induction concentrations, an activity dose-relationship is calculated.

The different sensitizing methods used and the performance in various laboratories made it difficult to compare animal data on the most important preservatives used. Unfortunately, even for the most widely used preservatives, only an incomplete

Table 7. Concentration ranges of frequently used preservatives (biocides) in paints, adhesives and cleaning products in Switzerland

| Preservative                       | Concentration ranges in paints and adhesives (ppm) | Concentration ranges in cleaning products (ppm)               |
|------------------------------------|----------------------------------------------------|---------------------------------------------------------------|
| MCI (MCI/MI)                       | 1–30                                               | 1–30                                                          |
| remarks:                           | about 10% lie in the range 30–100                  | 12% of products for public use lie in the range 1000–3000 ppm |
| BIT <sup>a)</sup>                  | 30–1000                                            | 1–3000                                                        |
| 2-chloroacetamide                  | 30–3000                                            | 1–3000                                                        |
| 2-chloro-N(hydroxymethyl)acetamide | 1–1000                                             | 1–1000                                                        |
| BHT <sup>a)</sup>                  | 10–10,000                                          | 100–10,000                                                    |
| oethilnone                         | 30–3000                                            | 100–3000                                                      |

<sup>a)</sup> MCI: 5-chloro-2-methyl-4-isothiazolin-3-one; BIT: benzisothiazolinone; BHT: butylated hydroxytoluene.

set of published data on predictive test results is available; a summary of such results is shown in Table 6.

The strong sensitizing activity of MCI/MI is shown in guinea pigs as well as in the mouse lymph node assays. In comparison, the sensitizing activity of BIT is much lower; e.g., an induction concentration of 5% in the maximization test sensitized 3 out of 20 treated animals, and in the LLNA, only concentrations of 10% and higher induced a significant proliferation of the lymph nodes. This difference in sensitizing activity between BIT and MCI/MI is shown in a direct comparison by Botham et al. (32). In another publication with direct comparison between MCI and BIT, the minimal concentration inducing a significant proliferation in the LLNA was 10.4% for BIT and 0.01% for MCI/MI (35).

Predictive human tests with preservatives were also published. Tests with MCI showed that volunteers became sensitized when a concentration of 20 ppm or higher was used during induction (35, 36). BIT induced sensitization when 725 ppm was used during induction, but not when 360 ppm was used during induction (35). Chloroacetamide induced a high incidence of reactions in 2 different tests according to the Draize protocol: 35/205 and 47/150 positive reactions (37, 38).

### Conclusions

The literature review has shown that cosmetics are still the most important exposure area for the risk of induction of sensitization to MCI/MI. On the other hand, the use of MCI/MI in such a large number of products industrially and domestically has shown that the risk of exposure to MCI/MI from paints is also increasing and that the number of airborne reactions to MCI/MI in already-sensitized patients can be expected to increase in the future.

Several actions may help to prevent such an increase in reactions to MCI/MI from industrial products. Predictive testing of chemicals allows the ranking of chemicals by their allergenic potential. To replace MCI/MI by a less sensitizing preservative would help to prevent provocation reactions to MCI/MI in paints. However, it has to be remembered that the distribution of a compound is also an important factor and that reactions to less allergenic compounds may also increase when such compounds are much more widely distributed than today.

In addition to the allergenic potential and the distribution of a chemical, the concentration of preservatives used in products is important to obtain an idea of the possible safety margin between

the concentration in products and the minimum concentration required to induce allergies. For MCI/MI, the use concentrations in cosmetics are in the range of 7.5 to 15 ppm, for industrial products, 15–55 ppm, concentrations being under discussion in the EU. Concentrations of 30–50 ppm MCI/MI already induced a significant proliferation in mouse lymph nodes (33) or allergic skin reactions in guinea pigs (31).

Table 7 shows the ranges of product concentrations according to the chemical product register of the Swiss Federal Office of Public Health. Based on the wide range of concentrations used, no safety factor specific for one preservative can be calculated; the safety factor must be calculated for each product. It is noteworthy that, for MCI, some household products with which repeated skin contact with the undiluted product is to be expected, have been found to contain concentrations of MCI up to  $100 \times$  higher than those allowed in cosmetics (e.g., household cleaning products).

About 80% of the product concentrations lie in the given ranges. (The search was performed using classes with the following boundaries: 1 ppm, 10 ppm, 30 ppm, 100 ppm, 300 ppm, 1000 ppm, 3000 ppm and 10000 ppm).

Declaration of ingredients in chemical products and the use of separate preservatives in cosmetics and in chemical products would also help to avoid situations as have occurred with MCI/MI. Iodopropynyl butylcarbamate (IPBC) has been used for many years as fungicide and bactericide for the preservation of wood only, without induction of allergic reactions. It is now also used in cosmetics and contact allergic reactions may therefore arise in the future (39).

Another possible way of reducing the number of reactions to MCI/MI is its inactivation by sodium bisulfite, as the studies of Gruber (40, 41) and Bohn et al. (17) have shown. Bisulfite reacts with MCI and MI in opening the ring structure and reducing the allergenic properties of the chemicals. This would reduce the time of exposure to MCI/MI after painting, and reduce the risk of allergic reactions to MCI/MI in already-sensitized individuals. Technical problems, especially unwanted chemical reactions with other ingredients in the matrix may, however, limit the general use of sodium bisulfite in the inactivation of MCI/MI.

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