

Isothiazolinones in commercial products at Danish workplaces

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Summary

Background. In recent years, a steep increase in the frequency of occupational contact allergy to isothiazolinones has been reported from several European countries.

Objective. To examine the extent and occurrence of isothiazolinones in different types of product at Danish workplaces.

Methods. Seven different isothiazolinones were identified in the *Dictionary of Contact Allergens: Chemical Structures, Sources, and References* from Kanerva's *Occupational Dermatitis*. By use of the chemical names and Chemical Abstracts Service numbers for these chemicals, information on products registered in the Danish Product Register Database (PROBAS) was obtained.

Results. All seven isothiazolinones were registered in PROBAS. The top three isothiazolinones registered were: benzisothiazolinone (BIT), registered in 985 products, methylisothiazolinone (MI), registered in 884 products, and methylchloroisothiazolinone (MCI)/MI, registered in 611 products. The concentration ranges were 0.01 ppm to 45% for BIT, 0.01 ppm to 10% for MI, and 0.01 ppm to 14.1% for MCI/MI. The most common product type was 'paint and varnish'; five of the seven isothiazolinones were registered in this type of product.

Conclusion. Isothiazolinones are present in multiple products registered for use at workplaces, and may occur in high concentrations.

Key words: 2-methyl-4,5-trimethylene-4-isothiazolin-3-one; allergic contact dermatitis; benzisothiazolinone; dichlorooctylisothiazolinone; isothiazolinones; methylchloroisothiazolinone; methylisothiazolinone; octylisothiazolinone.

Knowledge regarding the individual and general exposures to hazardous chemicals in our environment is pivotal for understanding the individual and general

disease risk related to these chemicals. Such information is also essential for the planning of preventive initiatives. Information on the production and use of the chemicals may be retrieved from national and international statistical offices, databases, and manufacturers; this data collection is difficult and time-consuming. The Scandinavian countries have developed registers that contain information on the contents of hazardous chemicals in products registered for occupational use in the respective countries.

The isothiazolinones are preservatives (Table 1) that have been in use for > 30 years in products for both

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occupational and consumer use (1). This group of chemicals was soon recognized as containing strong or extremely potent allergens (2). Nevertheless, these chemicals were permitted (Table 1), and registered in different product categories (3). The general argument made in risk assessment has been that even extremely potent contact allergens can be used safely in products if the exposure concentration is sufficiently low (4). The risk assessment methods rest primarily on animal assays such as the guinea-pig maximization test (GPMT) (5) or the local lymph node assay (LLNA) (6, 7), and/or experimental induction studies in humans (human repeated insult patch test) (8). However, these methods have either failed or been incorrectly interpreted with regard to fulfilling the expectations of safety in terms of the risks of sensitization (1, 6, 7, 9, 10). The consequences have been serious, and have given rise to numerous occupational cases of severe allergic contact dermatitis (11–17) and an epidemic of contact allergy resulting from the use of cosmetic products caused by methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI) (1, 18–21).

In view of the above, we provide an overview of the occurrence of isothiazolinones in registered chemical products, and discuss the clinical and general health implications.

Methods

Identification of allergens

We selected the isothiazolinones listed in the *Dictionary of Contact Allergens: Chemical Structures, Sources, and References* from Kanerva's *Occupational Dermatitis* (33).

In the examination of product types registered with content of the isothiazolinones, the chemical names and the Chemical Abstract Service (CAS) numbers for these isothiazolinones were searched for in the Danish Product Register Database (PROBAS) (September 2012).

The Danish Product Register Database

PROBAS is a database in which the composition of, primarily, hazardous chemical products for occupational use is registered. Products are registered: (i) if the product/substance is manufactured or imported for occupational use in a quantity of > 100 kg annually; (ii) if the product contains at least one chemical that is registered as harmful according to the Danish Ministry of the Environment and the Danish Working Environment Authority (WEA); (iii) if the product contains $\geq 1\%$ of the

substance (for preservatives, the limit is 0.1%); (iv) if the product/substance is assigned an occupational exposure limit in the WEA list of limit values for substances and materials; and/or (v) if materials contain $\geq 1\%$ of a substance that has been assigned an occupational exposure limit in the WEA list of limit values for substances and materials (34). When a product is registered in PROBAS, we assume that it is used in the Danish work environment.

PROBAS is updated at the end of every odd year with data collected from the manufacturers in even years. In cases where there were fewer than three manufacturers, the specific product types were classified as confidential.

In PROBAS, the chemicals are categorized according to the Use Categories Nordic (UCN) code system (35). The system is the same in Norway, Sweden, and Denmark. The system consists of main groups and subgroups. The code for the main group consists of three characters, and the code for the subgroup consists of the main group plus three digits. One chemical can have more than one UCN code. According to the principal manufacturer of MCI/MI, MCI is not sold as an independent substance, so, even though it is listed on its own in PROBAS, it is likely to be used together with MI.

All confidential information was omitted from the dataset. No main groups were deleted, but subgroups that had a ratio of < 2% between the main group and the subgroup were deleted by the authors to maintain a more relevant overview.

Results

The isothiazolinones included in this study are shown in Table 1. All seven isothiazolinones were registered in PROBAS. The results of the search in the database for different types of registered product are shown in Tables 2 and 3. The concentrations listed in the two tables are in the same format as used in PROBAS. It is not possible to compare the different product types, because some of them are raw materials and others are products for the downstream user.

Benzisothiazolinone (BIT) (CAS no. 2634-33-5)

BIT was registered in 985 different products registered in PROBAS, and was the isothiazolinone most often found in products registered in PROBAS. The top three product types containing BIT were paints and varnishes (544), cleaning/washing agents (108), and polishing agents (65). BIT was registered in concentrations from 0.01 ppm to 45%.

Table 1. Marketed isothiazolinones and their regulation

Isothiazolinones	CAS numbers	Regulations			
		Cosmetics	REACH	CLP	BPR
Benzisothiazolinone (INCI) (1,2-benzisothiazolin-3-one)	2634-33-5	Not allowed (22, 23)	Intended but not registered (24)	Harmonized classification: R43/H317 with specific concentration limit: 0.05% (25)	Review programme: PT 2, 6, 9, 11, 12, and 13 (26) Non-included: PT 7, 10, and 22 (27)
4,5-Dichloro-2-n-octyl-4-isothiazolin-3-one	64359-81-5	Not allowed (23)	Intended but not registered (24)	Not classified	Approved: PT 8 Review programme: PT 7, 9, 10 11, and 21 (26) Non-included: PT 6, and 12 (27) Not allowed
2-Methyl-4,5-trimethylene-4-isothiazolin-3-one	82633-79-2	Not allowed (23)	–	Harmonized classification: R43/H317 (25)	Not allowed
Methylchloroisothiazolinone (INCI) (5-chloro-2-methyl-4-isothiazolin-3-one)	26172-55-4	Not allowed (23)	Preregistered for 2010, but not registered (28)	Not classified	Not allowed
Methylchloroisothiazolinone (INCI) (5-chloro-2-methyl-4-isothiazolin-3-one) and methylisothiazolinone (INCI) (2-methyl-4-isothiazolin-3-one)	55965-84-9 and 96118-96-6	Allowed at 15 ppm (3:1) (29, 23)	Preregistered for 2010, but not registered	Harmonized classification: R43/H317 with specific concentration limit: 15 ppm (25) RoI France, concerning environmental classification: by end of 2014 (30)	First product: Review programme: PT 2, 4, 6, 11, 12, and 13 (26) Non-included: PT 3, 7, 9, and 10 (27) Second product: not allowed
Methylisothiazolinone (INCI) (2-methyl-4-isothiazolin-3-one)	2682-20-4	Allowed at 100 ppm (23, 31)	Preregistered for 2010, but not registered (28)	Harmonized classification: R43/H317 with non-specific concentration limit Inventory (self-classification): R43/H317 with specific concentration limit: 0.1%* Slovenia by end of 2013 (32)**	Review programme: PT 2, 6, 11, 12, and 13 (26) Non-included: PT 4, 7, 9, 10, and 22 (27)
Octylisothiazolinone (INCI) (2-n-octyl-4-isothiazolin-3-one)	26530-20-1	Not allowed (23)	Preregistered for 2010, but not registered (28)	Harmonized classification: R43/H317 with specific concentration limit: 0.05% (25)	Review programme: PT 6, 7, 9, 10, 11, and 13 (26) Non-included: PT 4, 8, and 12 (27)

BPR, biocidal products regulation; CLP, the regulation on classification, labelling and packaging of substances and mixtures; INCI, International Nomenclature of Cosmetic Ingredients; PT, product type; REACH, Registration, Evaluation, Authorization and Restriction of Chemical substances; RoI, registry of intention – ‘warning’ of future proposal.

*According to CLP there is non-specific concentration limit for MI but according to the inventory there is a “self-classification” with a specific concentration limit on 0.1%. This concentration is not validated or authorized but is used by some manufactures because of the allergenic potency of MI. For those manufacturer this concentration will be effective from 1st of June 2015.

**The European Commission requested Slovenia to classify MI according to the Annex XV dossier in REACH. The deadline was December 2013.

Methylisothiazolinone (CAS no. 2682-20-4)

MI was the second most frequently registered isothiazolinone, with 884 different products registered in PROBAS. The top three product types

containing MI were paints and varnishes (471), cleaning/washing agents (87), and polishing agents (60). MI was registered in concentrations from 0.01 ppm to 10%.

Table 2. The results from the Danish Product Register Database (PROBAS) for benzisothiazolinone, methylisothiazolinone, methylchloroisothiazolinone, and methylchloroisothiazolinone/methylisothiazolinone

Main group	Benzisothiazolinone; CAS no. 2634-33-5						Methylisothiazolinone; CAS no. 2682-20-4						Methylchlorisothiazolinone; CAS no. 26172-55-4						Methylchlorisothiazolinone/ methylisothiazolinone; CAS no. 55965-84-9							
	No. of products in group	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)
Absorbents and adsorbents	90	3	3.3	75	0.1	369	6	6.7	4	0.02	147	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Air cleaners and anti-odour agents	45	-	-	-	-	-	6	6.7	4	0.02	147	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biocides	1174	26	2.2	0.04	45	5.5*	34	2.9	0.05	10	1.1*	25	2.1	0.11	17.2	0.9*	27	2.3	0.03	14.1	1.6*	-	-	-	-	-
Car care products	96	21	21.9	2.5	5.4	0.26*	18	18.8	2	0.008	33.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Binding agents	366	20	5.5	0.6	0.1	201	21	5.7	0.4	0.138	182	5	1.4	0.9	0.01	21.4	19	5.2	4.71	0.01	23.3	-	-	-	-	-
Binding agents for paints, adhesives, etc.	184	15	4.1	0.6	0.1	254	14	3.8	8	0.138	282	-	-	-	-	-	10	2.7	11	0.01	24.2	-	-	-	-	-
Other binding agents	168	-	-	-	-	-	-	-	-	-	-	4	1.1	0.9	0.01	21.3	8	2.2	4.71	0.004	21.7	-	-	-	-	-
Softeners	59	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	8.5	12	0.01	33.8	-	-	-	-	-
Other softeners	32	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	6.8	12	0.01	38.8	-	-	-	-	-
Colouring agents	324	25	7.7	12.5	1	486	36	11.1	0.25	0.05	56.4	22	6.8	0.75	0.01	38.8	7	2.2	1.4	0.015	29.2	-	-	-	-	-
Pigments for paints and printing inks	191	16	4.9	12.5	0.1	265	25	7.7	1.4	0.01	50.5	17	5.2	4.2	0.01	46.1	4	1.2	1.4	0.001	8.7	-	-	-	-	-
Other colouring agents	125	8	2.5	14.7	1	0.13*	10	3.1	0.25	0.05	83.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Flooring materials	146	6	4.1	93.9	0.05	199	5	3.4	7.5	0.05	137	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Impregnation/proofing	122	7	5.7	10.5	0.03	126	8	6.6	1.36	0.013	22.1	4	3.3	0.01	0.0037	10.0	-	-	-	-	-	-	-	-	-	-
Cosmetics	484	-	-	-	-	-	9	1.9	0.75	0.085	174	-	-	-	-	-	8	1.7	0.01	0.003	4.9	-	-	-	-	-
Construction materials	201	3	1.5	500	0.29	0.13*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Adhesives	752	28	3.7	0.23	0.10	173	17	2.3	0.5	0.023	47.6	6	0.8	0.96	0.003	7.6	24	3.2	0.09	0.05	30.9	-	-	-	-	-
Paint and varnish	3567	544	15.3	0.01	0.33	176	471	13.2	0.01	0.085	36.3	275	7.7	0.01	0.07	12.9	363	10.2	0.01	3.9	103	-	-	-	-	-
Paint: water-based, decorative/ protection, industrial use	219	144	4.0	0.01	0.05	196	110	3.1	0.01	0.024	20.3	75	2.1	0.04	0.001	1.5	105	2.9	0.02	0.022	25.4	-	-	-	-	-
Paint and varnishes: additives	77	6	7.8	0.55	0.03	118	7	9.1	0.86	0.018	65.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Metal surface treatment remedies	468	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	0.9	40	0.2	816	-	-	-	-	-
Solvents	797	-	-	-	-	-	4	0.5	1	0.1	251	4	0.5	3	0.1	254	-	-	-	-	-	-	-	-	-	-
Surface active agents	517	16	3.1	0.1	0.04	73.2	16	3.1	0.53	0.01	36.0	6	1.2	0.98	0.001	6.0	5	1.0	2.7	0.001	7.6	-	-	-	-	-

Table 2. Continued

Main group	Benzisothiazolinone; CAS no. 2634-33-5						Methylisothiazolinone; CAS no. 2682-20-4						Methylchloroisothiazolinone/methylisothiazolinone; CAS no. 55965-84-9					
	No. of products in group	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group
Surface treatment for paper, cardboard, and other non-metals	106	3	2.8	0.15	0.02	56.4	4	3.8	1.35	0.012	47.8	3	2.8	3.6	0.01	37.3	8	7.5
Surface treatment for paper and cardboard	73	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	5.7
Polishing agents	350	65	18.6	0.66	0.04	76.9	60	17.1	0.25	0.024	31.3	20	5.7	0.15	0.9	433	32	9.1
Polishing agents for lacquers (car wax)	93	18	5.1	0.78	0.02	57.4	22	6.3	1.4	0.024	60.1	7	2.0	4.2	0.07	281	-	-
Wax and other polishing preparations for floors	81	27	7.7	0.66	0.02	51.3	24	6.9	0.25	0.009	9.41	10	2.9	0.39	0.001	5.4	18	5.1
Other polishing agents	71	9	2.6	35.4	0.04	194	-	-	-	-	-	-	-	-	-	-	-	-
Cleaning/washing agents	3560	108	3.0	0.06	0.17	83.4	87	2.4	0.02	0.19	55.8	34	1.0	0.03	0.6	156	50	1.4
Cracking indicators	56	2	3.6	0.75	0.0045	30.3	-	-	-	-	-	-	-	-	-	-	-	-
Rust inhibitors	421	11	2.6	0.7	0.06	90.7	12	2.9	0.01	0.06	48.8	3	0.7	0.04	0.001	3.4	-	-
Corrosion inhibitors	169	10	2.4	0.7	0.06	93.0	-	-	-	-	-	-	-	-	-	-	-	-
Raw materials and intermediate products	572	-	-	-	-	-	3	0.7	75	0.01	91.7	-	-	-	-	-	-	-
Rinsing agents	95	11	11.6	160	0.1	263	3	3.2	1.8	0.0004	3.56	6	6.3	2.3	0.001	6.1	-	-
Rinsing agents (for dishwashing machines)	50	-	-	-	-	-	3	3.2	1.8	0.0004	3.56	3	3.2	5.3	0.001	9.9	-	-
Lubricants	1225	3	0.2	0.21	0.02	127	-	-	-	-	-	-	-	-	-	-	5	0.4
Toners	56	10	17.9	26.4	0.05	271	6	10.7	3.9	0.049	98.3	-	-	-	-	-	4	7.1
Printing inks	293	10	3.4	8	0.13	413	14	4.8	2.4	0.07	62.1	12	4.1	7.4	0.07	65.6	13	4.4
Filling agents	956	16	1.7	5.4	0.17	206	18	1.9	0.28	0.1	78.8	13	1.4	0.76	0.5	343	8	0.8
Viscosity changers	71	-	-	-	-	-	3	4.2	9.9	0.005	30.0	-	-	-	-	-	-	-
Total	-	985	-	0.01	45	-	884	-	0.01	10	-	474	-	0.01	17.2	-	611	-

* Percentages.

Table 3. The results from the Danish Product Register Database (PROBAS) for dichlorooctylisothiazolinone and octylisothiazolinone

Main group	No. of products in group	Name Dichlorooctylisothiazolinone; CAS no. 64359-81-5					Name Octylisothiazolinone; CAS no. 26530-20-1				
		No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)
Biocides	1174	12	1	0.11*	28.1	11.1*	16	1.4	7.1	16	1.7*
Binding agents	366	–	–	–	–	–	2	0.5	10	0.02	71.2
Cooling agents for metal processing	201	–	–	–	–	–	3	1.5	100	0.03	177
Adhesives	752	–	–	–	–	–	4	0.5	67.5	16.3	4.1*
Paint and varnish	3567	38	1.1	405	0.2	0.11*	60	1.7	0.02	0.1	177
Filling agents	956	5	0.5	94	0.1	368	5	0.5	25	0.5	0.13*
Total	–	58	–	94	28.1	–	111	–	0.02	16.3	–

*Percentages.

Methylchloroisothiazolinone/methylisothiazolinone (CAS no. 55965-84-9)

MCI/MI was the third most frequently registered isothiazolinone, with 611 different products registered in PROBAS. The top three product types containing MCI/MI were paints and varnishes (363), cleaning/washing agents (50), and polishing agents (32). MCI/MI was registered in concentrations from 0.01 ppm to 14%.

Methylchloroisothiazolinone (CAS no. 26172-55-4)

MCI was the fourth most frequently registered isothiazolinone, with 474 different products registered in PROBAS. The top three product types containing MCI were paints and varnishes (275), cleaning/washing agents (34), and biocides (25). MCI was registered in concentrations from 0.01 ppm to 17%.

Octylisothiazolinone (OIT) (CAS no. 26530-20-1)

OIT was the fifth most frequently registered isothiazolinone, with 111 different products registered in PROBAS. The top three product types containing OIT were paints and varnishes (60), biocides (16), and filling agents (5). OIT was registered in concentrations from 0.02 ppm to 16.3%.

Dichlorooctylisothiazolinone (DCOIT) (CAS no. 64359-81-5)

DCOIT was registered in 58 different products, which was the second lowest number among the isothiazolinones in this study. The top three product types containing DCOIT were paints and varnishes (38), biocides (12), and filling

agents (5). DCOIT was registered in concentrations from 94 ppm to 28.1%.

2-Methyl-4,5-trimethylene-4-isothiazolin-3-one (MTMIT) (CAS no. 82633-79-2)

MTMIT was the only isothiazolinone for which all of the use categories (UCN codes) were confidential. The chemical was registered in seven products in concentrations from 47.6 to 150 ppm.

Discussion

The present study shows that thousands of products are registered in PROBAS as containing isothiazolinones.

BIT and MI were registered in 985 and 884 products, respectively; MCI/MI was registered in 611 products.

The most prominent product type containing these three isothiazolinones was paints and varnishes (with a total of 3567 products), in which BIT, MI and MCI/MI were the predominant isothiazolinones. This is in accordance with clinical experience (Table 4), where isothiazolinone allergies have been reported in painters (36–39) and paint production workers (12, 40, 41). It is also known that MCI/MI and MI may evaporate and cause airborne allergic contact dermatitis, a manifestation that has been increasingly seen with particular MI-preserved paints (36–38, 42). MI and BIT have been found to cause airborne contact dermatitis, respiratory symptoms, including acute asthma, and systemic allergic contact dermatitis (15, 36). The presence of MI in paints was further highlighted in a study in which, of 19 different water-based paints from the Danish retail marked, all contained MI, four contained MCI, and 16 contained BIT (43). The emission of BIT, MCI and MI from paint has also been shown (43).

Table 4. Clinical effects of cutaneous and airborne exposures to the isothiazolinone preservatives

Exposures	Concentrations	Clinical symptoms	Duration of eczema/ consequence	Reference
Cosmetic products	MCI/MI < 15 ppm MI < 100 ppm	Allergic contact dermatitis: face and hands	One event: 4–6 months Repeated events: chronic disease	(18–21)
Paint, glues, oils, etc.	MCI/MI < 14 ppm MI < 300 ppm BIT < 360 ppm (43)	Severe allergic contact dermatitis: face and hands Airborne dermatitis, respiratory symptoms	6–12 months Change or loss of job	(11–14, 36–38, 42, 44–46)
Biocides	MCI > 0.5% MI > 0.5% BIT > 0.5%	Chemical burns, generalized severe allergic contact dermatitis with subjective symptoms Systemic contact dermatitis, respiratory symptoms	Chronic disease, risk of disability	(11, 15, 45)
Airborne exposure	Probably < 60 mg/m ² (43)	Primary sensitization may be possible Flare-ups of facial and systemic contact dermatitis	Acute and chronic disease	(15, 36–38, 42, 43, 47)

BIT, benzisothiazolinone; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

Preservative exposure from paints has changed since 2000, when MI was introduced as a stand-alone preservative and, to some extent, replaced MCI/MI. The reason may be that, whereas MCI/MI is on the list of dangerous substances, labelled R43/H317 (may cause sensitization), and has to be declared on the label if it is present in amounts > 15 ppm, no such requirements exist for MI (Table 1); instead, there is self-classification, with a specific concentration limit of 0.1% in industrial products (25). This may erroneously lead the manufacturers to assume that MI is unproblematic (29).

The products registered with the highest content of isothiazolinones were car care products, BIT being present in 21.9% of products, and MI in 18.8%; a similar pattern was seen for polishing agents for cars and floor products (Tables 2 and 3). We have not found any reports concerning contact allergy related to the use of such products.

Contact allergy to isothiazolinones in the paper and textile industry has also been reported (14, 17, 48, 49). In our study, BIT, MI and MCI/MI were registered in products for the surface treatment of paper, cardboard, and other non-metals, although not very frequently. In the paper industry, they may be present in the concentrated biocides that are used and added to the pulp. All of the isothiazolinones were registered as biocide products. This is a product group that may have multiple uses.

Contact allergy to BIT and OIT has been reported in metalworkers (50); these are also the two allergens found in cooling agents by chemical analysis in a Finnish study (51). In PROBAS, only OIT was registered in cooling agents for metal processing (Table 3). This emphasizes

the importance of patch testing with these special isothiazolinones in metalworkers with occupational eczema.

Exposure to high concentrations of isothiazolinones (Table 4) can cause chemical burns followed by contact sensitization resulting from a single exposure (52–57). Further accidental exposure to such high concentrations may lead to generalized dermatitis accompanied by systemic contact dermatitis and subjective symptoms (15). Such cases may develop into chronic diseases.

A part of the problem is that much emphasis and reliance has been put on the results of animal assays, in particular the LLNA, to predict the sensitization potency of these substances. The reporting of these results is very brief in the scientific literature, as EC3 values only, not supported by data, and has also been shown to be misleading (9). This is in contrast to the amount of human data from the occupational setting and consumers, which, for a long period of time, have been ignored by industry and regulators.

In three product categories, namely paints and varnishes, biocides, and filling agents, all six isothiazolinones were registered, whereas, for all other product categories, some but not all isothiazolinones were used.

There are only few studies on cross-reactions between the different isothiazolinones. In 1992, Damstra et al. found, in an analysis of 556 patch tested patients, that 8 of 10 patients who reacted to BIT also reacted to MCI/MI, and 8 of 56 patients who reacted to MCI/MI also reacted to BIT (58). In a recent study, Mose et al. found that all patients with concomitant positive patch test reactions to OIT, BIT and MCI/MI were painters, which suggests concomitant sensitization rather than

cross-reactivity (16). Cross-reactivity can only be studied in animals or if the primary sensitizer in humans is known. In GPMTs, it was shown that cross-reactivity between MCI and MI exists, whereas no cross-reactivity could be shown between MCI, MI as primary sensitizer, and OIT, and probably BIT (59). In 2008, Isaksson et al. also showed, by testing workers accidentally sensitized to MCI, that cross-reactivity between MCI and MI is likely, depending on the degree of contact allergy (60), which is in accordance with clinical experience (61). This means that, in detecting cases of contact allergy to isothiazolinones, one cannot rely on testing only with MCI and MI in the baseline series.

It is very important for the physician and the clinical procedure that all information concerning the product be on the product label and/or in the Material Safety Data Sheet (MSDS) or other product datasheets, so that exposures to allergens can be identified, appropriate patch testing performed, and the correct diagnosis made. Otherwise, important allergens can be missed. The correct diagnosis is very important for patients with occupational allergic contact dermatitis, both for the medical prognosis and for the compensation, depending on national laws (62).

In conclusion, isothiazolinones are present in multiple products registered for use at the workplace, and may occur in high concentrations. BIT was the most frequent isothiazolinone, being registered in the most products (985), and the concentration range was 0.01 ppm to 45%.

Knowledge of the use and exposure to the isothiazolinone preservatives, together with the contact allergic potential and the clinical disease related to the exposure, leads to the following points to be addressed:

- The use concentrations in the different exposure scenarios need to be revised.
- All types of isothiazolinone, independently of concentration, should be labelled on the product and included in the MSDS.
- The use of concentrated solutions of isothiazolinones should only be permitted in closed systems, and the workers involved need proper education.
- Is the margin of safety for isothiazolinones so low that future use should be abolished?

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