

NOTES

RD₅₀ Value as the Criterion for Setting Maximum Admissible Levels of Occupational Exposure to Irritants in Poland

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The aim of this work is to analyse Maximum Admissible Concentration (MAC) values proposed for irritants by the Group of Experts for Chemical Agents in Poland, based on the RD₅₀ value. In 1994–2004, MAC values for irritants based on the RD₅₀ value were set for 17 chemicals. For the purpose of the analysis, 1/10 RD₅₀, 1/100 RD₅₀ and the MAC/RD₅₀ ratio were calculated. The determined MAC values are within the 0.01–0.09 RD₅₀ range. The RD₅₀ value is a good rough criterion to set MAC values for irritants and it makes it possible to estimate quickly admissible exposure levels. It has become clear that, in some cases, simple setting the MAC value for an irritant at the level of 0.03 RD₅₀ may be insufficient to determine precisely the possible hazard to workers' health. Other available toxicological data, such as NOAEL (No-Observed-Adverse-Effect Level) and LOAEL (Lowest-Observed-Adverse-Effect Level), should always be considered as well.

RD₅₀ occupational exposure limit sensory irritation

1. INTRODUCTION

The value of the concentration of a chemical in the occupational environment constitutes the most important element used to characterise working conditions prevailing during a specific manufacturing process. In Poland, an Intersectoral Commission for Setting MAC Values was established in 1983 by the Minister of Health and Social Policy. The task of the Commission is to take independent regulatory decisions on the levels of chemical concentrations admissible in the occupational environment. The members of the Commission comprise representatives of the Ministry of Health, Ministry of Labour, experts of commercial organisations or companies, and scientific research institutions. Assessment of the sanitary and biological effects of chemicals in workplace atmosphere performed by a competent

team of experts seems to be an essential element of that process. The Group of Experts for Chemical Agents (GECA), affiliated to the Commission, comprises experts from various fields of science. In 1983–2004, GECA prepared and verified 468 MAC (Maximum Admissible Concentration) documentation sheets including 76 documentations to extend the Polish list of MAC values and adjust it to European Union requirements.

2. AIM

For a large number of chemicals, MAC values are based on their irritating activity. The aim of this work is to analyse MAC values proposed for irritants by the GECA, based on the RD₅₀ value representing the concentration that induces a 50% reduction in the respiratory rate.

3. SETTING OF MAC VALUES FOR IRRITANTS

Three categories of a Maximum Admissible Concentration (MAC, Polish equivalent: NDS) are specified in Poland:

- MAC (Maximum Admissible Concentration): the time-weighted average concentration for a conventional 8-hr workday and workweek defined in the Labour Code, to which workers may be exposed during their whole working life, without any adverse effects on their health (also when retired) or that of the next generations.
- MAC-STEL (Maximum Admissible Short-Term Concentration): an average concentration, to which workers may be exposed without any adverse health effects if it does not last longer than 15 min and does not occur more than twice during a workday, at intervals not shorter than 1 hr.
- MAC-C (Maximum Admissible Ceiling Concentration): ceiling concentration, which because of the threat to workers' health or life, should not be exceeded even instantaneously.

In 1994, GECA developed uniform principles for setting MAC values, described in detail by Czerczak [1]. Between 1994 and 2004 using those uniform criteria GECA experts proposed irritation-based MAC values for 124 chemicals.

GECA experts prepare documentation specifying proposed MAC values for chemicals based on most recent literature data. The documents comprise data on physical and chemical characteristics, presence, applications, exposure, biological activity, a list of current hygienic standards valid in Poland and some other countries, assessment of health hazards, and the basis for the proposed MAC values. The documentation of the MAC values for occupational exposure is prepared according to the following procedure: published results of studies are used to determine NOAEL (No-Observed-Adverse-Effect Level) or LOAEL (Lowest-Observed-Adverse-Effect Level). Then, the MAC value is calculated using the uncertainty factor, which is a product of five coefficients to allow for inter-species differences and the route of administration, inter-individual

differences in human susceptibility, switch from short-term to prolonged exposure, use of LOAEL instead of NOAEL, experts' uncertainty about the completeness of the data, and possible remote effects.

Irritants are characterised by rapid, or threshold, activity and the risk of the changes after exposure to an irritant is associated with exceeding, even for a short time, a threshold concentration value rather than with the value of mean concentration during a work shift. The organs most sensitive to irritants are the skin, eyes, and respiratory mucosa. Changes in those organs enable determination of the aforementioned parameters which are used to set the values of hygienic standards. Inhalatory exposure to irritants causes a physiological response where there is contact as a result of excitation of olfactory nerve endings. The sensation of irritation in the nasal cavity may be accompanied by a subjective feeling of irritation in the throat as a result of excitation of the laryngeal nerve endings. Those reactions induce changes in the lower respiratory tract resulting in a reduction in the breathing rate. The disturbed breathing efficiency, one of the main effects of irritants, may be described by the RD_{50} value, which is used as a basis for setting the values of hygienic standards [2, 3].

Alarie [2, 3] reports irritating effects of chemicals in humans at concentrations equivalent to RD_{50} , $0.10 RD_{50}$, and $0.01 RD_{50}$. In his opinion, predicted values of the admissible occupational exposure level remain within the 0.01 – $0.10 RD_{50}$ range. A MAC value at the level of $0.03 RD_{50}$ is the maximum admissible value which can be accepted.

4. RESULTS

In 1994–2004, MAC values for irritants based on the RD_{50} value were set for 17 chemicals (Table 1). This was followed by an analysis of MAC values proposed by GECA for the indicated 17 irritants. For the purpose of the analysis, $0.10 RD_{50}$, $0.01 RD_{50}$, and the MAC/RD_{50} ratio were calculated. Mean values of the factor relating MAC values to the RD_{50} value for the examined chemicals were also determined. The calculated value of that factor

is equal to 0.03 and, in accordance with Alarie's suggestion, the values of the proposed hygienic standards are within the 0.01–0.10 RD₅₀ range. The determined MAC values are within the 0.01–0.09 RD₅₀ range. The latter range comprises the values determined for the 17 chemicals, while for seven of those chemicals the MAC value is equal to exactly 0.03 RD₅₀. The seven chemicals are acrolein, ethylamine, isophorone, propionic acid, isopropyl acetate, *n*-pentyl acetate, butylamine. MAC values at a level above 0.03 RD₅₀ were proposed for four chemicals: *n*-propyl acetate, isoamyl acetate, methyl-*n*-amyl acetate, and diisobutyl ketone. None of the values is higher than the lower value of 0.01 RD₅₀ proposed by Alarie.

MAC values at the lowest level (0.01 RD₅₀) were set for the following 5 chemicals: *p*-benzoquinone, benzaldehyde, hexanal, methyl-*tert*-butyl-ether, isobutyraldehyde. Here is a discussion of the data

serving as the basis for setting the MAC values at a level below the mean value.

- For *p*-benzoquinone, there are two reasons why it would not be reasonable to use the corresponding fraction of RD₅₀ as the sole basis for MAC value setting:
 - *p*-benzoquinone, like some isocyanates, differs from the majority of irritants in that the breathing rate reduction is relatively permanent. *p*-Benzoquinone at 0.10 RD₅₀ causes accumulation of the effects already after exposure repeated 3 to 5 times [2, 13];
 - experimental data on the systemic activity of *p*-benzoquinone are not available. Such activity may be expected only in the haematopoietic system.

Therefore, GECA experts proposed that additional two uncertainty factors be adopted:

TABLE 1. Registry of Chemicals for Which Group of Experts for Chemical Agents (GECA) Proposed RD₅₀-Based MAC Values in 1994–2004

CAS No.	Chemical	MAC (mg/m ³)	MAC-STEL (mg/m ³)	RD ₅₀ (mg/m ³)	1/100 RD ₅₀ (mg/m ³)	1/10 RD ₅₀ (mg/m ³)	MAC/RD ₅₀	Year	Reference
66-25-1	hexanal	40	80	4290	42.9	429	0.01	2004	4
1634-04-4	methyl- <i>tert</i> -butyl-ether	180	270	16600	166	1660	0.01	2003	5
107-02-8	acrolein	0.05	0.1	2	0.02	0.2	0.03	2002	4
75-04-7	ethylamine	9.4	18	278	2.78	27.8	0.03	2002	6
109-60-4	<i>n</i> -propyl acetate	200	400	3323	33.23	332.3	0.06	2000	7
123-92-2	isoamyl acetate	250	500	5612	56.12	561.2	0.04	1999	8
78-59-1	isoforone	5	10	157	1.57	15.7	0.03	1999	7
110-43-0	methyl- <i>n</i> -amyl ketone	238	475	4770	47.7	477	0.05	1999	9
79-09-4	propionic acid	30	not established	1161	11.61	116.1	0.03	1998	10
108-21-4	isopropyl acetate	600	1000	17785	177.85	1778.5	0.03	1998	7
123-86-4	butyl acetate	200	950	8336	83.36	833.6	0.02	1997	11
78-84-2	isobutyraldehyde	100	not established	8867	88.67	886.7	0.01	1997	4
106-51-4	<i>p</i> -benzoquinone	0.1	0.4	20	0.2	2	0.01	1996	2, 3
628-63-7	<i>n</i> -pentyl acetate	250	500	8200	82	820	0.03	1996	10
108-83-8	diisobutyl ketone	150	300	1665	16.65	166.5	0.09	1995	9
109-73-9	butylamine	10 (ceiling)	not established	362	3.62	36.2	0.03	1995	12
100-52-7	benzaldehyde	10	40	1470	14.7	147	0.01	1994	4
Mean value MAC/RD ₅₀							0.03		

Notes. MAC—Maximum Admissible Concentration, MAC-STEL—Maximum Admissible Short-Term Concentration.

a factor associated with interindividual differences of sensitivity in humans (at the level of 2) and a modifying factor related to the experts' estimate of data completeness (at the level of 3).

- Considering that benzaldehyde, in addition to the irritating and sensitising activity, at high concentrations also acts as a narcotic, while at low concentrations it has a depressing effect on the central nervous system and impairs the breathing function, a short-term exposure limit (STEL) value of 0.03 RD_{50} [5] was set.
- For hexanal, no literature data could be located to justify setting the MAC value at 0.01 RD_{50} [14].
- For methyl-*tert*-butyl ether, the MAC value was additionally justified by the results of studies on the effects of that chemical on the reproduction and development of rats, for which the inhalatory NOAEL value had been set at 1440 mg/m^3 [15]. When deriving the MAC value from NOAEL, the following uncertainty factors were used: the factor of 2 associated with different interindividual sensitivity, the factor of 2 associated with the differences between species, and the "expert" factor of 2 [14].
- Animal toxicity data additionally made it possible to derive the MAC value for isobutyraldehyde from the LOAEL value at 2940 mg/m^3 . At that concentration, the chemical caused only slight changes in the nasal mucosa of the rats. As much as 5 uncertainty factors were used in the calculations and the total factor was 32 [16].

A MAC value at the level of 0.09 RD_{50} was proposed for one chemical, diisobutyl ketone. When setting the MAC for that chemical, results of sub-acute toxicity studies on mice and guinea pigs were also taken into account [17]. It had been demonstrated that a 6-week exposure to diisobutyl ketone vapours at 728 mg/m^3 did not result in any changes, and the value was adopted as NOAEL.

The MAC value proposed for butylamine is a ceiling value. The value was set at the level of 0.03 RD_{50} [14].

6. CONCLUSIONS

The RD_{50} value is a good rough criterion to set MAC values for irritants; it makes it possible to estimate quickly admissible exposure levels in the occupational environment. The use of that value seems to be particularly suitable for irritants for which no MAC values have been set yet. It has become clear that, in some cases, simple setting the MAC value for an irritant at the level of 0.03 RD_{50} may be insufficient to determine precisely the possible hazard to workers' health. Other available toxicological data associated with exposure to those chemicals, such as NOAEL, LOAEL, and the dependence of the observed effects on the concentration of the chemical in the air, should always be considered as well.

As the next stage, it seems advisable to compare the MAC values based on NOAEL or LOAEL, which GECA experts propose for irritants by, with the corresponding values based on RD_{50} as the criterion for setting MAC values.

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