

ORIGINAL ARTICLE

Dimethyl sulphate; a hidden problem in occupational medicine

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Occup Environ Med 2004;**61**:73–75

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14 February 2003**Background:** In a chemical plant, alkylating agents (mainly ethylene oxide and propylene oxide, but also dimethyl sulphate) are utilised for the production of special surfactants.**Aims:** To determine possible uptakes of dimethyl sulphate by workers using N-methylvaline.**Methods:** Sixty two workers in a chemical plant (38 smokers, 24 non-smokers) with potential exposure to dimethyl sulphate were monitored with respect to their blood levels of N-methylvaline. Ten laboratory workers without exposure to methylating agents were controls. Blood samples of eight workers from a specific working area were analysed for N-methylvaline in a follow up investigation four months later.**Results:** The 95th centile for N-methylvaline was 80.7 µg/l blood in the exposed workers compared to 12.4 µg/l blood in controls. In a hot spot area, 10 workers exceeded the German exposure equivalent value for dimethyl sulphate (40 µg/l blood) up to fourfold. In contrast, dimethyl sulphate has not been detectable in workplace air in this area. In a follow up investigation of eight of these 10 workers, N-methylvaline levels were significantly lower, but still increased.**Conclusions:** The present study is to our knowledge the first to report increased N-methylvaline levels after occupational exposure to dimethyl sulphate. As ambient monitoring values in the plant could not explain this exposure, skin contact was considered to be the main route of uptake for this substance. Dimethyl sulphate may therefore represent an occupational problem that has been generally underestimated in the past.

Dimethyl sulphate is an industrial chemical that is used widely as an alkylating agent to convert compounds such as phenols, amines, and thiols to the corresponding methyl derivatives. It is used for the manufacture of methyl esters, ethers, and amines in dyes, drugs, surfactants, perfumes, pesticides, or other organic chemicals.¹

In Germany, dimethyl sulphate is produced in a single factory at a volume of about 10 000 t per year, which are distributed and further processed in about 50 plants.² Dimethyl sulphate has been classified as a probable human carcinogen (group 2A) by the IARC.³ The Deutsche Forschungsgemeinschaft (DFG) has also rated dimethyl sulphate as a group 2 carcinogen. The technical exposure limit value (TRK) is 200 µg/m³ in workplace air for the use of this chemical.⁴

Besides its carcinogenic properties, dimethyl sulphate is also known to be very irritant to mucous membranes because of its rapid hydrolysis in water to methanol and sulphuric acid.² The primary routes of potential occupational exposure to this substance are inhalation and dermal contact.¹

The absorbed amounts of this direct alkylating agent can react with DNA (especially methylation of N-7 and O-6 of guanine and N-3 of adenine) or protein targets like the N-terminal valine in erythrocyte globin in order to form N-methylvaline.^{5,6} The DFG has evaluated a correlation between the concentration of dimethyl sulphate in ambient air and the concentration of N-methylvaline in globin. Such exposure equivalents for carcinogenic working materials (EKA) allow an estimation of the internal exposure. For this reason, biomonitoring data from workers handling dimethyl sulphate were directly correlated with the concentration of this substance in workplace air. These values for N-methylvaline were later extrapolated to the current TRK value of 200 µg/m³. According to this correlation, an exposure to 200 µg/m³ dimethyl sulphate (the current German TRK value) corresponds to 40 µg/l blood N-methylvaline.⁴ Thus,

this EKA value represents a threshold limit value that must not be exceeded by workers under reasonable working conditions in compliance with the TRK value.

However, this value could only be extrapolated from very few data on external and internal exposures to dimethyl sulphate.^{4,6} In fact, despite its large production volume and the carcinogenic properties of this chemical, there are only few data available in the literature on occupational exposures and biological monitoring. Our study may contribute to closing this gap.

In the chemical plant we examined, the low volatile dimethyl sulphate is used, besides other alkylating substances such as ethylene oxide and propylene oxide, as the principal chemical for the production of surfactants for textile industry. Within health supervision of the workers, we investigated the internal exposure of the workers using the corresponding globin adducts as parameters of biochemical effects. The primary focus of our study has been the biological monitoring of ethylene and propylene oxide, because exposure seemed most probable to these substances due to their high volatility in comparison to dimethyl sulphate.⁷ Though dimethyl sulphate could not be detected in workplace air, we decided to determine the globin adduct of this substance as well in order to investigate a possible uptake via skin. The results for that parameter are presented in this paper.

METHODS

Collectives

A total of 62 employees (7 females, 55 males) of the chemical plant producing surfactants for textile industry took part in

Abbreviations: IARC, International Agency for Research on Cancer; DFG, Deutsche Forschungsgemeinschaft; TRK, technical exposure limit; EKA, exposure equivalent for carcinogenic working materials

Main messages

- Analysis of N-methylvaline in the blood of workers of a chemical plant revealed a massive exposure to dimethyl sulphate in a specific building of the plant.
- Ambient monitoring underestimates exposure to dimethyl sulphate.
- Skin absorption may be the main route of uptake for this substance.
- Although the N-terminal valine of haemoglobin is methylated by endogenous processes, N-methylvaline is a suitable and sensitive parameter for biochemical effect monitoring of persons exposed to dimethyl sulphate.

this study; 38 were smokers, and 24 were non-smokers. The age of the workers was 19–59 years with a median age of 35 years. All of the employees stated that they wear protective gloves during their work.

Eight workers in a hot spot area (as revealed by the first investigation) took part in a follow up investigation four months later. The median age of this subgroup (four smokers, four non-smokers) was 36 years (range 28–54 years).

The alkylating substances (ethylene oxide, propylene oxide, or dimethyl sulphate) processed in the plant are pumped via pipeline into sealed vessels for reaction with various compounds (for example, fatty acids, phenols, or alcohols). The reaction products are then finally filled into barrels or containers.

Stationary air monitoring in this area has been conducted regularly by the company itself as well as by the German Berufsgenossenschaft using an official GC/MS method with a limit of detection of 10 µg dimethyl sulphate/m³.⁸

The control group consisted of 10 persons (2 females, 8 males) from our laboratory with no exposure to dimethyl sulphate or other methylating agents. Two of these persons were smokers, eight were non-smokers. The median age of the control group was 30 years (range 27–59 years).

Adduct monitoring

The biological adduct monitoring was conducted according to the method recommended by the Deutsche Forschungsgemeinschaft.⁹ After isolation of erythrocytes and globin from the blood, the level of N-methylvaline was quantified using the modified Edman procedure with N-methylvaline-leucine-anilide as calibration standard and N-ethoxy-ethyl-valine-alanine-anilide as internal standard. The formed pentafluorophenyl thiohydantoin derivatives were finally determined and quantified with mass spectrometric detection (EI mode) after gas chromatographic separation on a DB-17 HT capillary column (crosslinked (50%-phenyl)-methylpolysiloxane, 30 m×0.25 mm ID, 0.15 µm film thickness, J & W Scientific, Folsom, CA, USA).

The resulting data were expressed as micrograms adduct per litre blood, as the German exposure equivalent is also expressed in this unit. For comparison with other determinations, 10 µg N-methylvaline/l blood is considered equivalent to 525 pmol adduct/g globin.

For quality control purposes, blood of a smoker and a non-smoker has been included in each analytical series. The between series precision (n = 8) has been determined to be 7.9% for the smoker (mean concentration 12.2 µg/l blood) and 6.9% for the non-smoker (mean concentration 9.2 µg/l blood).

Policy implications

- Results stress the need for biological monitoring of workers handling working materials such as dimethyl sulphate which can be taken up via skin.
- In accordance with the large production volume and its carcinogenic properties, more studies about the actual internal exposure of workers handling dimethyl sulphate should be taken into consideration.

RESULTS

Table 1 summarises the results. The internal exposure of a group of workers is illustrated in the relative cumulative frequency for N-methylvaline depicted in fig 1. Figure 2 presents the results of our follow up study of eight workers with high internal exposure to dimethyl sulphate.

DISCUSSION

As shown in fig 1, 52 of the 62 workers (85%) showed N-methylvaline levels in the range of the general population that do not differ significantly (p = 0.1, Wilcoxon test, two tailed) from the values obtained from our control group (especially regarding the different smoking habits). However, our study revealed a massive exposure to dimethyl sulphate in a group of 10 employees working in a specific building of the chemical plant, where this substance is processed. This shows that the exposure is strictly localised in this area. The values for N-methylvaline in blood of these workers even exceeded the exposure equivalent value for dimethyl sulphate up to fourfold (see fig 1).

These results were quite surprising, because stationary air monitoring of dimethyl sulphate in this area performed both by the company itself as well as by official authorities showed only values below the limit of detection (10 µg/m³). This obviously led to an underestimation of the actual burden of the workers.

As a possible reason for these high exposures, skin contact with residues of unreacted dimethyl sulphate in the product was assumed. Since this hot spot could be identified by use of biological monitoring, it was decided to further investigate the internal exposure of these workers in order to control the efficiency of preventive measures.

In the second investigation four months after the first, only 8 of the 10 workers with the highest internal burdens that had already participated in the first study took part. Two employees did not participate in this follow up study for various reasons.

As shown in fig 2, the N-methylvaline levels of this subgroup of workers were still increased in the follow up, but significantly lower for most of the workers (p = 0.05, Wilcoxon test, two tailed). After the results of our first study, the company had taken measures to reduce the exposure. The reaction and stirring times for the product were prolonged in order to diminish dimethyl sulphate residues. Furthermore, a

Table 1 N-methylvaline levels in blood of workers potentially exposed to dimethyl sulphate (n = 62) and controls (n = 10)

	N-methylvaline (µg/l blood)		
	Median	95th centile	Max. value
Workers (n=62)	11.6	80.7	184.7
Controls (n=10)	9.7	12.4	12.9

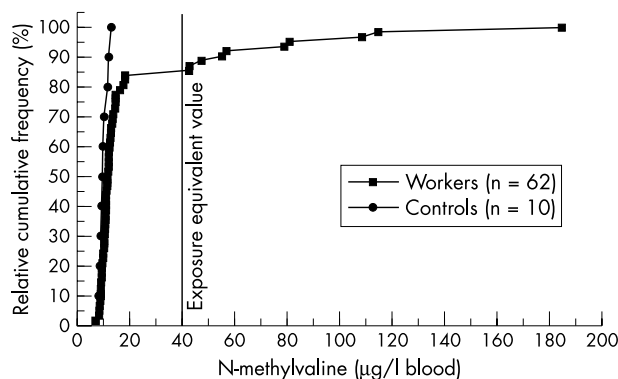


Figure 1 Relative cumulative frequency for N-methylvaline in blood of workers and controls.

bushing was introduced for the suction tube of the pump so as to minimise skin contact when filling barrels with reaction products. Beyond that, the exhausting possibilities were improved and workers were advised to wear protective helmets with external air supply during opening of the reaction vessel. Apparently, these measures appeared successful in improving the exposure situation of the workers. Thus, the median value for the haemoglobin adduct of dimethyl sulphate in these eight workers decreased from 79.8 µg/l blood to 36.4 µg/l blood in the follow up, although three workers still exceeded the level of the exposure equivalent.

Normal levels for N-methylvaline in the general population have already been reported in the literature.^{10–12} The physiological sources of this background level are probably endogenous methylation with S-adenosylmethionine. Smoking habits also had an influence on N-methylvaline levels, apparently due to methylating agents present in tobacco smoke (for example, nitrosamines).¹¹ Most recent publications showed median levels for non-smokers of about 8.5 µg/l blood and for smokers of about 11 µg/l blood, which is in good agreement with the values found in our control group and most of the workers (see table 1).¹²

As far as we are aware, this is the first study to report such excess levels of N-methylvaline after occupational exposure to dimethyl sulphate in a subgroup of workers. Ambient monitoring was insufficient for an estimation of the real exposure levels of workers. The vapour pressure of dimethyl sulphate is quite low; air monitoring of this substance requires highly sensitive methods and has several shortcomings. Dimethyl sulphate may be hydrolysed by air humidity on the sorbent material or may easily react with other compounds present in ambient air (for example, alcohols, amines, etc) and therefore evade quantification.²

The German commission for the investigation of health hazards of chemical compounds in the work area has investigated the relation between the concentration of carcinogens in the workplace air and that of the substance or corresponding adducts in biological material. From these relations, the body burden which results from uptake of the substance exclusively by inhalation may be determined. Basing on this linear relation established for dimethyl sulphate, the maximum value for N-methylvaline found in the blood of the workers would correspond to an inhalative exposure to more than 1000 µg dimethyl sulphate/m³ air.^{4–6}

Dermal absorption seems to be the most probable route of uptake in this case. We therefore question whether ambient monitoring is still a reasonable way of estimating occupational exposure to dimethyl sulphate. As air monitoring does not reflect all routes of uptake, it may consequently underestimate total exposure and hence suggest a “safe” workplace when this is not the case.

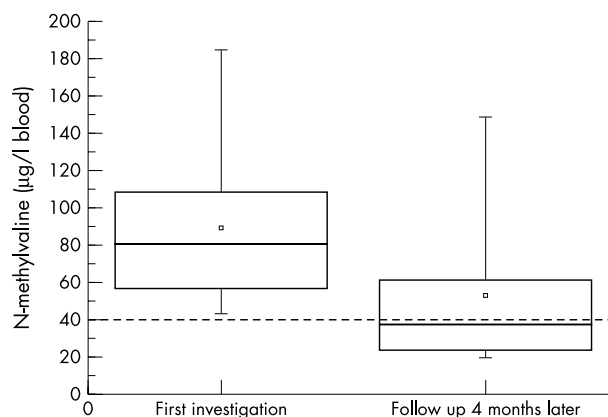


Figure 2 N-methylvaline levels of eight workers with high internal burden in the first investigation compared to the follow up four months later. The broken line indicates the EKA value for dimethyl sulphate of 40 µg/l blood.

Our results stress the need for biological monitoring of workers handling compounds which are taken up via the skin. Considering the high production volume, the very scarce literature on this compound and the toxicological profile, dimethyl sulphate may indeed represent a “hidden” problem in occupational medicine that deserves closer attention.

ACKNOWLEDGEMENTS

We wish to thank the Berufsgenossenschaft Chemie for their support in conducting our study.

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REFERENCES

- 1 National Institute of Health Sciences, National Toxicology Program. 9th report on carcinogens. <http://ehis.niehs.nih.gov/roc/ninth/rahc/dimethylsulfate.pdf> (status March 2002).
- 2 TRGS 901. Begründungen und Erläuterungen zu Grenzwerten in der Luft am Arbeitsplatz, Ausgabe April 1997: TRK-Werte für Dimethylsulfat (BArbBl 9/82, S. 96). http://www.umwelt-online.de/recht/t_regeln/trgs/trgs900/901/an4.htm (German, status: March 2002).
- 3 IARC. Dimethyl sulphate. *IARC Monograph Eval Carcinog Risks Hum* 1999;71:575–89.
- 4 DFG (Deutsche Forschungsgemeinschaft). *List of MAK and BAT values 2001*. Commission for the investigation of health hazards of chemical compounds in the work area, report no. 37. Weinheim: Wiley-VCH, 2001.
- 5 Mathison BH, Taylor ML, Bogdanffy MS. Dimethyl sulphate uptake and methylation of DNA in rat respiratory tissues following acute inhalation. *Fund Appl Toxicol* 1995;28:255–63.
- 6 Lewalter J. N-alkylvaline levels in globin as a new type of biomarker in risk assessment of alkylating agents. *Int Arch Occup Environ Health* 1996;68:519–30.
- 7 Schettgen T, Broding HC, Angerer J, et al. Haemoglobin adducts of ethylene oxide, propylene oxide, acrylonitrile and acrylamide—biomarkers in occupational and environmental medicine. *Tox Letters* 2002;134:65–70.
- 8 Hauptverband der gewerblichen Berufsgenossenschaften, ed. *Von den Berufsgenossenschaften anerkannte Analysenverfahren zur Feststellung der Konzentrationen krebserzeugender Arbeitsstoffe in der Luft in Arbeitsbereichen—Stand Juli 1997*. Köln: Carl Heymanns Verlag, 1997.
- 9 Angerer J, Schaller KH, eds. *Analyses of hazardous substances in biological materials*. Vol. 5, Deutsche Forschungsgemeinschaft. Weinheim: VCH, 1996.
- 10 Törnqvist M, Ostermann-Golkar S, Kautiainen A, et al. Methylations in haemoglobin from monozygotic twins discordant for cigarette smoking: hereditary and tobacco-related factors. *Chem Biol Interact* 1992;82:91–8.
- 11 Bader M, Lewalter J, Angerer J. Analysis of N-alkylated amino acids in human haemoglobin: evidence for elevated N-methylvaline levels in smokers. *Int Arch Occup Environ Health* 1995;67:237–42.
- 12 Thier R, Lewalter J, Selinski S, et al. Re-evaluation of the effect of smoking on the methylation of N-terminal valine in haemoglobin. *Arch Toxicol* 2001;75:270–3.



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