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NIOSH Comments to DOL

COMMENTS OF THE
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
ON
THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION
ADVANCE NOTICE OF PROPOSED RULEMAKING ON
HEALTH AND SAFETY STANDARDS; OCCUPATIONAL EXPOSURE TO
2-METHOXYETHANOL, 2-ETHOXYETHANOL AND THEIR ACETATES

29 CFR Part 1910
Docket No. H-044

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

July 31, 1987

The National Institute for Occupational Safety and Health (NIOSH) has reviewed the Occupational Safety and Health Administration (OSHA) advance notice of proposed rulemaking (ANPR) on health and safety standards; occupational exposure to 2-methoxyethanol (2-ME), 2-ethoxyethanol (2-EE), and their acetates (2-MEA and 2-EEA), and offers the following comments.

A. Health Effects

An extensive bibliography is attached that provides OSHA with essentially all of the studies presently available from published sources. This bibliography is submitted in response to parts (a), (b), and (c) of question (1).

(1) What studies should OSHA consider to assess potential health risks, especially the reproductive and developmental effects, of 2-ME, 2-EE, 2-MEA, and 2-EEA?

(a) What available data, such as medical records or unpublished studies not now in the record, should be included in OSHA's decision making?

NIOSH has conducted semen analyses in support of a cross-sectional clinical and environmental evaluation of shipyard painters by Dr. Laura Welch at Yale University (currently at George Washington University School of Medicine) and those results have been provided to Dr. Welch. The results of Dr. Welch's study have been submitted for publication to the American Journal of Industrial Medicine. A NIOSH Health Hazard Evaluation (HHE) was also performed at the same time, and extensive data on environmental monitoring and levels of ethylene glycol ether metabolites in urine were collected. Another manuscript describing the results of this study has also been submitted to the American Journal of Industrial Medicine. A NIOSH HHE (HETA 84-415-1688) also was conducted in a Portland, Oregon foundry where there was exposure to EGEE. That HHE report is available, and a manuscript has been submitted by Ratcliffe et al. to the British Journal of Industrial Medicine. Those reports contain data on environmental monitoring, urinary excretion of 2-EE metabolites, and describe an association between reduced semen quality and exposure to 2-EE.

(b) In light of the reproductive, developmental, and hematotoxic effects shown by the animal studies, what human data show such effects?

NIOSH is not aware of any definitive studies of human populations that have experienced teratogenic outcomes as a result of exposure to either 2-ME, 2-EE, or their acetates. One study is suggestive of terata but NIOSH does not consider that study to be adequate support,

on its own, for a new standard (Syrovdko and Malysheva: Gig Tr Prof Zabol 4:25, 1977). There are several other studies that are suggestive of testicular toxicity (Cook et al.: Arch Environ Health 37:346, 1982 and HETA 84-415-1688, NIOSH 1986).

Several investigators have described hematotoxicity among humans:

Cohen: Am J Ind Med 6:441, 1984.
Cullen: Arch Environ Health 38:347, 1983.
Donely: J Ind Hyg Tox 18:571, 1936.
Greenberg: J Ind Hyg Tox 20:134, 1938.

Donely, Greenberg, and others have also reported toxic encephalopathy:

Parsons: J Ind Hyg Tox 20:124, 1938.
Zavon: Am Ind Hyg Assoc J 24:36, 1963.

These citations are also contained in the attached bibliography.

(c) What recent animal toxicity data for glycol ethers other than 2-ME, 2-EE and their acetates exist?

See attached bibliography.

(2) What dermal absorption studies are available and what is the extent of potential adverse health effects resulting from such dermal exposure?

OSHA is referred to the attached bibliography. Particular attention should be given to Ohi and Wegman (J Occ Med 20:675, 1978) and Dugard et al. (Environ Health Perspect 57:193, 1983). Dermal absorption has the potential of being the most significant route of human exposure, and could be responsible for human toxic responses under conditions that might appear to be safe if judged solely on the basis of airborne concentrations.

(3) What studies and other evidence are available indicating the combined effects of inhalation and dermal exposures?.

NIOSH is not aware of any studies that have explored the effects of simultaneous dermal and inhalation exposure. However, any effects would be expected to be related to the total absorbed dose. We will continue searching for such information.

(4) How should OSHA estimate the significance of risk at the current exposure levels for the 4 subject glycol ethers?

Specifically:

(a) What mathematical models are most appropriate to quantify the risk of reproductive and developmental effects or other adverse health effects from exposure to glycol ethers?

(b) What approaches, other than quantitative risk assessment, are available for assessing reproductive or developmental risks?

The following is in response to (4)(a) and (4)(b).

There are a variety of models suitable for conducting quantitative risk assessments. The risk assessment conducted by the Environmental Protection Agency represents one such approach. NIOSH is also developing a risk assessment in cooperation with Dr. Dale Hattis at the Massachusetts Institute of Technology. Dr. Hattis is attempting to rely heavily on pharmacokinetic data. NIOSH will make this risk assessment available to OSHA as soon as possible.

(c) Is EPA's use of margins of safety an appropriate method? Why? What are its advantages and/or disadvantages?

The use of margins of safety is appropriate when data are not suitable for a more precise approach such as a quantitative risk assessment.

(d) Which studies should be used for quantitative risk assessment for glycol ethers?

(e) Which health effects in which animal species, by which route(s) of administration and at which dose level(s), should be selected for use?

The following responds to (4)(d) and (4)(e).

The health effect that occurs at the lowest exposure concentration (or dose) should be used as the basis for risk assessment. Exposure limits should be established to prevent the most sensitive indicator of toxicity. The results of exposure by all routes of administration can be used to develop a quantitative risk assessment if doses are converted to common units such as mg/kg body weight. As OSHA has done in the past, care must be taken to thoroughly explain all assumptions that were made in conducting the risk assessment. Since OSHA has had much experience with the conduct of risk assessments, these will not be repeated here.

(f) How should dose levels in experimental animal studies be converted to equivalent doses for occupationally exposed persons? How should the dose levels be expressed?

Doses from various studies should be converted to mg/kg body weight unless there is compelling data supporting the use of other corrections such as surface area.

(g) What exposure duration other than working lifetime, i.e., gestation period, first trimester, etc., should be incorporated into a risk assessment model?

For developmental toxicity (teratogenicity) to occur in experimental animals a single exposure is sufficient to induce malformations and fetal death. The same potential should be assumed to exist for humans. Therefore, acute exposure must be considered to be equal in importance to working lifetime exposure. During pregnancy (particularly the first trimester), episodes of acute skin exposure may be of greater significance than the average inhalation exposure. Single exposures have also induced testicular toxicity in animal models, so the concern for acute exposures extends to males. Thus, models describing effects due to long term exposures may be inadequate for use in describing reproductive effects that result from short term exposure.

(h) Should corrections be made for species to species extrapolation and for combined routes of exposure (i.e., dermal and inhalation)? How should these extrapolations be done?

As stated in response to (4)(f), exposure data obtained from different species should be normalized. Corrections based on mg/kg body weight appear to be appropriate. NIOSH recommends that, when there are data demonstrating the ability of a substance to be absorbed through the skin, the amount of material absorbed by the dermal route should be added to the amount of material absorbed by inhalation to arrive at the total dose. Whenever possible, only the total dose should be used in modelling.

(i) Are there data available to indicate a "dose response" effect for glycol ether exposure?

(j) What is the relationship between frequency and duration of exposure to glycol ethers and risk of reproductive developmental effects?

The following is in response to items (i) and (j).

NIOSH believes that the most relevant data are those that describe terata (Horton et al.: Toxicol Appl Pharmacol 80:108, 1985, and Hardin and Eisenman: Teratology 35(3):321-328, 1987) and adverse testicular effects (Chapin et al.: J Androl 5:369, 1984; Foster et al.: Toxicol Appl Pharmacol 69:385, 1983; Foster et al.: Environ Health Perspect 57:207, 1984) in rodents following a single exposure by gavage. Signs of other toxic responses following these exposures were not observed. Though the testicular effects may be reversible (a transient decline in semen quality), effects on pregnant women may include fetal death or birth defects.

(k) What quantitative methods are available for estimating risks other than reproductive or developmental risks that are associated with glycol ether exposures (e.g., hematological effects, neurological effects)?

See the response to A(1)(b).

(l) What methods are available to measure the health risks from dermal contact with the glycol ethers?

NIOSH is not aware of any methods that can be used to discriminate between exposure by inhalation and dermal absorption. The determination of ethylene glycol ether metabolites in urine may provide an indication of total absorbed dose from all routes of exposure. However, because of uncertainties surrounding the kinetics of uptake, metabolism and excretion, these data cannot be used to develop a precise dose response curve. Although complete blood counts may provide an indication of hematologic effects, Cullen et al. (Arch Environ Health 38:347, 1983) have suggested that the ethylene glycol ethers may exert an effect on the marrow that will not be reflected by perturbations in the formed elements of blood.

B. Permissible exposure limits

The following responds to items (1) and (2).

2-ME and 2-MEA have been found to be more toxic than 2-EE and 2-EEA. Therefore, it may be necessary to set at least two permissible exposure limits within one standard, one for 2-ME and 2-MEA, and one for 2-EE and 2-EEA. The development of two separate standards should not be necessary because of the similarities in the adverse effects, the similarity in route of exposure, and the fact that in many situations, several of the ethers and their acetates are used simultaneously.

(1) Should OSHA set 4 separate PELs within one standard or set one PEL for all 4 substances?

Since the "potencies" of these four compounds are not equal, it may be difficult to promulgate a standard that assumes equivalent toxicity. However, such an approach would certainly facilitate development of a standard, compliance monitoring, and worker training. Thus, as stated above, it seems reasonable to attempt development of a single standard that sets forth one PEL for 2-ME and 2-MEA and one PEL for 2-EE and 2-EA. In the NIOSH Current Intelligence Bulletin (CIB) on glycol ethers, concern was expressed for the adverse effects that may result from exposure to other ethylene glycol ethers.

(2) Would compliance with limits for these four chemicals be facilitated by the promulgation of a single limit for all four chemicals, based on the hazards associated with the most toxic chemical (i.e., 2-ME)?

(3) Should the glycol ethers 2-ME, 2-MEA, 2-EE, and 2-EEA be treated separately or as a group in terms of rulemaking?

These glycol ethers can be treated as a group for the purposes of rulemaking, but a single PEL would not be appropriate.

(4) Should OSHA take a generic approach to the regulation of the family of glycol ethers and include other glycol ethers in the scope of its rulemaking?

Although NIOSH agrees that such a generic approach would constitute a prudent public health practice, we believe that data are insufficient to develop PELs for glycol ethers other than 2-ME, 2-MEA, 2-EE and 2-EEA.

(5) Should a revised standard for 2-ME, 2-EE and their acetates include an 8-hour time weighted average, a short term exposure limit (STEL), a ceiling level, and an action level or some combination of these limits?

Because of our concern that even single exposures have led to adverse reproductive effects in animals, NIOSH recommends that PELs should address a short-term limit, an 8-hour time weighted average (TWA), and contain provisions to prevent skin contact. The need to prevent skin absorption may increase in significance as the airborne concentration is reduced.

(6) What permissible exposure limits should be proposed and what health evidence is available to support these limits?

NIOSH is presently developing a criteria document on glycol ethers that will include a recommendation for precise exposure limits. NIOSH will transmit the document to OSHA as soon as it is completed.

(7) What are the limits of detection and accuracy of the available methods of monitoring for each of the four glycol ethers under consideration?

The following NIOSH analytical methods are Attachments 2, 3, and 4:

Method	Analyte
1403	2-ME 2-EE
S39	2-MEA
1450	2-EEA

NIOSH has also examined the ability of several laboratories to analyze 2-EEA. Summary results of rounds 86 and 89 of the Proficiency Analytical Testing (PAT) Program follow:

PAT Round	Number of Laboratories	Relative Standard Deviations			
		Samples			
		1	2	3	4
86	80	21.8%	18.8%	23.0%	17.3%
89	66	19.8%	11.0%	12.6%	9.6%

These data indicate that the participating laboratories were able to improve their analytical techniques and the accuracy of their determinations, thereby reducing their inter- and intra-laboratory variation. This is supported by data that demonstrates an increase in the number of laboratories that reported data for determinations of 2-EEA that fell outside established proficiency limits.

PERFORMANCE LIMITS FOR PAT ROUND 86 SOLVENTS

Sample Type	Sample Number	Proficiency Limits (mg)		Outliers	
		Ref	Low - High	# Low	# High
2-EEA	1	0.3005	0.1042 - 0.4968	6	4
2-EEA	2	0.7339	0.3191 - 1.1487	7	7
2-EEA	3	0.2117	0.0655 - 0.3580	9	6
2-EEA	4	1.0819	0.5205 - 1.6432	6	7

PERFORMANCE LIMITS FOR PAT ROUND 89 SOLVENTS

Sample Type	Sample Number	Proficiency Limits (mg) Ref	Low - High	Outliers # Low	# High
2-EEA	1	0.2377	0.0965 - 0.3790	7	5
2-EEA	2	0.8819	0.5912 - 1.1725	15	10
2-EEA	3	0.5482	0.3403 - 0.7560	14	10
2-EEA	4	0.6640	0.4726 - 0.8555	13	14

(8) What data support the technological feasibility of achieving the permissible limits under consideration for the various job categories?

NIOSH is submitting four Walk-Through Survey Reports, six Industrial Hygiene Reports, and one Health Hazard Evaluation (Attachments 5-15). These reports describe various painting operations in which some glycol ethers and their acetates were present. These reports indicate that, in most cases, worker exposure to 2-ME, 2-EE, 2-MEA, 2-EEA and butyl glycol methyl ether were well below 5 ppm as 8-hour TWA concentrations.

We are also submitting data obtained from the National Occupational Exposure Survey and the National Occupational Hazard Survey that describe the type and frequency of use of controls in those workplaces where 2-ME, 2-MEA, 2-EE, and 2-EEA were found.

C. Production and Control Systems

NIOSH has no information on these issues other than the reports supplied in response to question D.8.

D. Substitution Availability

NIOSH has no information concerning specific substitutes for 2-ME, 2-EE and their acetates. We do, however, reiterate the conclusions of our CIB.

> "Although the test results for some structurally related glycol ethers reported in this bulletin seem to suggest less hazardous compounds, the testing is not yet sufficient to identify a substitute for 2-ME and 2-EE. Possible health effects and potential exposures of alternatives to 2-ME and 2-EE should be fully evaluated prior to selection."

E. Protective Equipment and Respirators

NIOSH has no comments on items (1), (2), (3), (4), (5)(b)-(e) and (6).

(5) OSHA is aware that butyl rubber may provide the best 8-hour protection against dermal contact with 2-ME, 2-EE and their acetates and that nitrile rubber is effective in splash (short term) situations.

(a) Have any other materials been tested and been found to be equally protective?

Attachment 16 is a study by Coyne et al. that examines the efficacy of a number of glove materials. Attachment 17 contains similar data developed by the Union Carbide Corporation.

(7) Under what conditions (e.g., exposure level, type of operation, duration of exposure) do employers presently provide protective equipment and respirators to their exposed employees?

In NIOSH CIB #39: The Glycol Ethers, with particular reference to 2-methoxyethanol and 2-ethoxyethanol, NIOSH recommended that exposure to the glycol ethers be reduced to the lowest extent feasible. Only the most protective respirators are consistent with that recommendation: self-contained breathing apparatus with full facepiece operated in the pressure-demand mode, or a combination respirator which includes a Type C supplied-air respirator with a full facepiece operated in the pressure-demand mode and an auxiliary self-contained breathing apparatus operated in the pressure-demand mode. If OSHA does not follow NIOSH's respirator recommendation, and permits the use of air-purifying respirators (APR), then the attached selection table can be used (Attachment 18). OSHA must also consider the issue of adequate warning properties when establishing respirator selection criteria. If the PELs that will be established by OSHA are below the odor threshold, NIOSH would recommend that only cartridge or canister respirators with effective end-of-service-life indicators be allowed for 2-ME, 2-EE, 2-MEA, and 2-EEA. We have also attached a copy of a study by Coyne et al. (Attachment 16).

F. Exposure and Monitoring

(1) What proportion of the workforce in each of the following sectors is exposed to 2-ME, 2-EE and/or their acetates? At what levels?

Attachments 19 and 20 provide estimates (by SIC code) of the number of workers potentially exposed to 2-ME, 2-EE, 2-MEA, and 2-EEA. These data were obtained by the National Occupational Hazard Survey. NIOSH has no comments on items (2)-(10).

G. Worker Training

NIOSH has no comments on these issues.

H. Medical Surveillance

(1) What illnesses or conditions attributable to glycol ethers have been observed?

The NIOSH CIB describes adverse reproductive effects (including terata and testicular atrophy), hematologic disorders and behavioral disorders.

(2) What elements are appropriate for inclusion in medical and clinical examinations performed to identify overexposed workers and/or to indicate the status of workers health?

(3) Are semen analyses included in medical surveillance programs for male workers exposed to glycol ethers?

The following responds to items H(2) and H(3).

NIOSH cannot recommend a specific battery of clinical tests that would be useful for medical monitoring for the ethylene glycol ethers. Semen analysis may be useful for epidemiologic studies, but not for individual medical monitoring. The "normal" range is wide and there is much individual variation, both long- and short-term. The predictive value of any finding for indicating an effect of glycol ether exposure would be quite low. Also, the technical problems involved in specimen preservation, processing and analysis, make semen analysis a poor candidate for a routine screening test.

I. Costs of Control Measures

NIOSH has no comment on these issues.

J. Environmental Effects

NIOSH has no comments on these issues.

K. Impact on Small Business Entities

NIOSH has no comments on these issues.

L. Duplication/Overlapping/Conflicting Rules

NIOSH has no comments on these issues.

M. Financial and Economic Profile

NIOSH has no comments on these issues.

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15. Supplementary Notes

16. Abstract (Limit: 200 words): This testimony summarizes comments made by NIOSH concerning the proposed rulemaking on health and safety standards related to occupational exposures to 2-methoxyethanol (109864), 2-ethoxyethanol (110805), and their acetates, 2-methoxyethylacetate (110496) and 2-ethoxyethylacetate (111159). The comments concern specific studies which OSHA should consider in assessing the potential health risks, especially the reproductive and developmental effects, of exposure to these compounds. This testimony also addresses which available data, such as medical records or unpublished studies should be included in the decision making process by OSHA. Animal toxicity data for glycol ethers other than these are cited in the bibliography as are articles related to the dermal absorption studies and potential adverse health effects resulting from dermal exposure. Studies dealing with the combined effects of inhalation and dermal exposure are cited along with information related to estimating the significance of risk at the current exposure level, mathematical models most appropriate to quantify the risks, margins of safety, quantitative risk assessment methods, selection of animal species and route and dose levels for administration, exposure period, dose/response effect, factors involved in setting permissible exposure limits, production and control systems, substitute chemicals, protective equipment, number of workers exposed, and medical surveillance.

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