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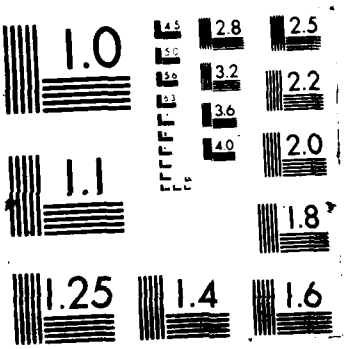
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TECHNICAL REPORT 8610

DRINKING WATER CRITERIA FOR THE GROUNDWATER POLLUTANT DIISOPROPYL METHYLPHOSPHONATE (DIMP)

JACK C. DACRE, Ph.D., D.Sc.
DAVID H. ROSENBLATT, Ph.D.

Prepared for

US Army Toxic and Hazardous Materials Agency

by

U S ARMY BIOMEDICAL RESEARCH & DEVELOPMENT LABORATORY
Fort Detrick
Frederick, MD 21701-5010

July 1987

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U S ARMY MEDICAL RESEARCH & DEVELOPMENT COMMAND
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19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Drinking water criteria for diisopropyl methylphosphonate (DIMP) for the protection of human health were calculated by the basic formula proposed by the US Environmental Protection Agency. The no-observable effect level (NOEL) was derived from the available toxicological data base for 90-day studies in the dog, rat, and mouse. It is recommended that the drinking water criterion for DIMP be set at 26.3 mg/L, based on an uncertainty factor of 100 and an extrapolation of the body weight of the dog being the most sensitive of the three animals evaluated.

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INTRODUCTION

This report provides recommendations for a definitive drinking water criterion on the compound diisopropyl methylphosphonate (DIMP). DIMP as a groundwater contaminant in the effluents presents an increasing environmental concern to the U.S. Army. We anticipate the need to update the toxicological and biological data base on DIMP, and develop both the effluent limits and the environmental exposure limits relating to the U.S. Army's pollution abatement and clean-up requirements.

Interim environmental criteria[1] had been derived for the following three compounds that had been identified as pollutants in both surface water and sampling wells on land at Rocky Mountain Arsenal, Colorado.[2]

1. Diisopropyl methylphosphonate (DIMP)

2. Isopropyl methylphosphonic acid (IMPA)

3. Dicyclopentadiene (DCPD)

The present report provides a definitive revision of the recommended interim drinking water criterion for one of these compounds, DIMP. This report was prepared in response to a request by the Office of the Surgeon General.[3]

CHEMICAL PROPERTIES OF DIMP

ALTERNATIVE NAMES

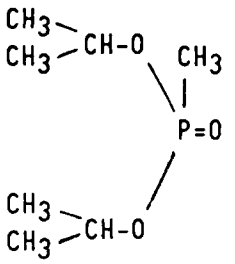
Diisopropyl methylphosphonate; DIMP; phosphonic acid, methyl-, bis-(1-methylethyl) ester (Chem. Abstr. after 1971); phosphonic acid, methyl-, diisopropyl ester (1947-1971); methanephosphonic acid, diisopropyl ester.

PHYSICAL AND CHEMICAL PROPERTIES

CAS Reg. No. 1445-75-6
Toxic Substances List: SZ9090000 (1983-1984 Supplement)
Edgewood Arsenal Number: EA 1250

Wiswesser Line Notation: 1Y&OPO&1&OY
Molecular formula: $C_7H_{17}O_3P$

Structural formula:



DIMP is a liquid at room temperature with n_D^{20} = 1.4112,[4] a bulk density at 25°C of 0.976 g/cc and a boiling point of 174°C.[5,6] Its vapor pressure-temperature behavior is closely approximated by the following empirical relationship.[5,6]

$$\text{Log P(mm of Hg)} = 9.8571 - 3105/T(^{\circ}K)$$

DIMP is best synthesized through the reaction of methyl iodide with triisopropyl phosphite.[7,8] Other methods are mentioned in the patent literature.[9-11]

The solubility limit of DIMP in water has not been determined. In studies of DIMP hydrolysis in acidic and basic solutions,[12] 0.12 N or higher DIMP was used at temperatures above 80°C, indicating solubilities of above 11 g/liter in that temperature range. In DIMP studies at Southern Research Institute,[13] the indicated solubility in water at 25°C was at least between 1 and 2 g/liter. Studies on the toxicity of DIMP to algae, however, utilized as much as 30.3 g/liter.[14]

DIMP hydrolysis rates in water at 98, 90, and 80°C have been reported as 2×10^{-6}, 0.88×10^{-6}, and 0.31×10^{-6} sec^{-1}, respectively.[15] The hydrolysis activation energy was estimated to be 26.9 Kcal/mole.[15] These reaction rates can be used to predict hydrolytic behavior at 10°C, a temperature more representative of groundwater in a temperate climate. The estimated rate is 3.2×10^{-11} sec^{-1}, corresponding to a hydrolysis half-life of about 687 years. In the studies cited above,[12] DIMP was among a series of alkylphosphonate esters whose hydrolysis characteristics were measured. In 1N HCl solution, rate constants of 1.74×10^{-4}, 2.81×10^{-4}, 4.78×10^{-4}, 8.53×10^{-4}, and 8.56×10^{-4} sec^{-1} were determined at 88.9, 94.4, 99.7, 104.8, and 105.9°C, respectively.[12] The acid hydrolysis appears to proceed by the S_N1 mechanism,

phosphonate esters. Basic hydrolysis appears to proceed by the S_N2 mechanism, since the DIMP hydrolysis rate is less than that of the lower alkylphosphonate esters. Typical rate constants for 0.12 N DIMP in 0.2N NaOH solution were 1.53×10^{-4}, 2.29×10^{-4}, and 4.82×10^{-4} M sec^{-1} at 80, 90, and 100°C, respectively. Basic hydrolysis at elevated temperatures is a convenient way to prepare the monoester, isopropyl methylphosphonate (IMP). In DIMP studies at Southern Research Institute,[13] the mono-sodium salt of IMP was prepared by dissolving DIMP in 2N NaOH, heating to 50°C, followed by slow cooling to room temperature, with stirring applied throughout the process. About 4 days were required for completion of the hydrolysis reaction. It would appear that at room temperature and mildly basic conditions, hydrolysis of DIMP would be quite slow. DIMP is formed from sodium isopropyl methylphosphonate at 270°, but DIMP is also converted, in part, to trimethylphosphine oxide at this temperature.[14,15] DIMP is decomposed almost entirely on short residence in a microwave plasma discharge;[16] among the products are methylphosphonic acid, isopropyl methylphosphonate, phosphoric acid, isopropyl alcohol, and propylene.

DIMP forms a number of metal complexes in the absence of moisture.[17-19]

For a summary of the analytical methods available for DIMP, the reader is referred to the 1975 report by Rosenblatt et al.[2]

MAMMALIAN TOXICOLOGICAL PROPERTIES OF DIMP

A summary of the acute toxicity of DIMP in various mammalian species is given in Table 1.

TABLE 1. SUMMARY OF ACUTE TOXICITY OF DIMP
IN VARIOUS MAMMALIAN SPECIES

Animal Species	Route of Administration	LD50 mg/kg (95% Confidence Limits)	References
Rat, male	Oral	1,125 (*)	20,21
female	Oral	826 (747-914)	
Rat	Subcutaneous	>200	22
Mouse, male	Oral	1,041 (903-1,201)	20,21
female	Oral	1,363 (1,165-1,594)	
Mouse	Intraperitoneal	>250	23
Rabbit	Subcutaneous	>100, <200	22
	Intravenous	224 (179-282)	24
	Dermal	>200	24
Duck, mallard	Oral	1,490	25
Quail, bobwhite	Oral	1,000	25
Mink	Oral	503	25
Calf	Oral	Ca. 750	26, 27

* The data did not permit calculation of confidence limits.

The acute toxicity of DIMP was determined for a wide variety of aquatic organisms representing several trophic forms. These included primary producer organisms, primary consumers, and secondary consumers. They were exposed under a wide variety of water quality conditions to a range between 257 and 6,332 mg/L.[28] The bioconcentration factor for DIMP was experimentally examined in fish; essentially no bioconcentration was observed for bluegills continually exposed to ^{14}C-DIMP.[28]

McPhail and Adie[29] have reported that intravenously injected DIMP did not inhibit cholinesterase in the blood of rabbits.

Contract studies by Hart[20,30] and others,[31,32] supported by the US Army Medical Research and Development Command, are described below. They provide a data base required for establishing environmental and occupational health criteria.

The Draize Eye Irritation Test[20] revealed significant signs of temporary irritation following the application of DIMP to the conjunctival sacs of the eyes of albino rabbits. The data indicated that grade 4 damage does clear within 24 hours and that irrigation with water, at both 2 and 4 seconds after application, completely prevented the irritation in the cornea and iris. In only one rabbit (no. 6147) of the three tested without irrigation was there a positive indication of eye irritation. Because of this anomalous result in the one rabbit, the test was repeated with technical grade DIMP, and a 10% aqueous suspension of DIMP. (See Appendix A for unpublished report).[31] The pure compound produced moderate corneal opacity lasting seven days, some conjunctival irritation, but no iritis. The aqueous suspension of DIMP produced no acute irritation of the cornea or conjunctiva of rabbit eyes. The acute dermal irritation study in rabbits indicated only minimal skin irritation following doses of 0.2, 0.63, and 2.0 g/kg DIMP to the abraded or intact skin.[21]

In the standard Draize guinea pig sensitization test, DIMP was not shown to be a strong skin sensitizer.[20] This test was also repeated with technical grade DIMP by the modified method of Buehler.[33] The compound did not induce a delayed contact hypersensitivity reaction in guinea pigs (See Appendix A for unpublished report).[31] A study was also made to determine the potential of DIMP for producing sensitization in humans by a patch test (See Appendix B for unpublished report).[32] Some 215 adult subjects were tested with a 10% suspension of DIMP in water. No evidence was found for the elicitation of pre-existing allergic contact dermatitis, or for the induction of allergic contact dermatitis in human subjects.

DIMP was tested in the Ames mutagenicity assay with five strains of Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and the Saccharomyces cerevisiae assay (strain D4), both with and without S9 activation. In both assays DIMP showed no mutagenic activity.[30]

DIMP was administered in the diet at doses of 100, 300, and 3,000 ppm to 20 pregnant female rats per dose level on days 6 through 15 of gestation. There were no changes in the dams or among the fetuses that would have indicated that the compound had any teratogenic effects. In a reproductive study in rats (20 per dose level), dietary incorporation of DIMP at levels of 300 and 3,000 ppm produced no dose-related reproductive responses for three successive generations with two matings per generation.[30]

A paralytic demyelination study in chickens (20 per group) that were given 500, 1000 or 1,500 mg/kg DIMP did not produce evidence of nerve fiber degeneration.[30]

Subchronic 90-day feeding studies were carried out in male and female rats, mice, and dogs.[20,30] Rats (32 males and 32 females per group) were given DIMP at dose levels of 300, 1,000, and 3,000 ppm; mice (30 males and 30 females per group) at dose levels of 210, 700, and 2,100 ppm, and beagle dogs (4 males and 4 females per group) at dose levels of 150, 1,500, and 3,000 ppm. All animals were examined daily, and weekly body weights and food consumption were obtained. At termination, all animals were grossly necropsied and approximately 27 different tissues taken for examination. The tissues from the control and high-level groups of animals were examined histologically. In all three species, no clear or meaningful changes were seen that could be ascribed to the ingestion of DIMP, and it was concluded that the compound produced no toxic effects at a dietary concentration of 3,000 ppm or below for the rats and dogs and 2,100 ppm for the mice, over the 90-day period of the study. The highest dose levels studied were used to calculate the NOELs, but it should be noted that these dose levels are probably not the highest possible NOELs under the conditions of the experiments.[20,30]

Several other studies on DIMP have been carried out by the Chemical Systems Laboratory, Edgewood Arsenal (now called Chemical Research, Development and Engineering Center), Aberdeen Proving Ground, MD. A single generation reproductive study in rats was reported by Hardisty et al.[34] They found no evidence of adverse effects upon the reproductive cycle of rats when the animals were exposed to 10 or 1,000 ppm DIMP in the drinking water. In a second study by Biskup et al.,[35] 20 male and 20 female rats at each concentration were exposed to DIMP at concentrations of 0.6 and 6 ppb, and at 10 and 1,000 ppm, in the drinking water continuously for 26 weeks. The results showed that DIMP had no effect on growth rate or water consumption, and produced no related gross or microscopic lesions after 26 weeks exposure to DIMP.

CALCULATION OF A DRINKING WATER CRITERION

Drinking water criterion values are calculated for DIMP, according to the methodology in Appendices C and D, as follows:

1. Dogs:

NOEL = 3,000 mg/kg in the feed x 0.025 day^{-1} (dose to feed concentration factor)[36]

= 75 mg/(kg body weight x day)

ADI = NOEL/Uncertainty Factor = 75 mg/(kg x day)/100

= 0.75 mg/(kg x day)

$$C_{drinking\ water} = \frac{0.75\ mg/(kg \times day) \times 70\ kg/man}{2\ L/(man \times day)}$$

= 26.25 mg/L

2. Rats:

NOEL = 3,000 mg/kg in the feed x 0.05 day (dose to feed concentration factor)[36]

= 150 mg/(kg body weight x day)

ADI = NOEL/Uncertainty factor = 150 mg/(kg x day)/100

= 1.5 mg/(kg x day)

$$C_{drinking\ water} = \frac{1.5\ mg/(kg \times day) \times 70\ kg/man}{2L\ (man \times day)}$$

= 52.5 mg/L

3. Mice:

NOEL = 2,100 mg/kg in the feed x 0.12 day^{-1} (dose to feed concentration factor)[36]

= 252 mg/(kg body weight x day)

ADI = NOEL/Uncertainty factor = 252 mg/(kg x day)/100

= 2.52 mg/(kg x day)

$$C_{drinking\ water} = \frac{2.52\ mg/(kg \times day) \times 70\ kg/man}{2\ L/(man \times day)}$$

= 88.2 mg/L

RECOMMENDED DRINKING WATER CRITERIA

Human drinking water criteria for DIMP calculated on an animal weight basis, and using an uncertainty factor of 100, are given in Table 2.

TABLE 2. HUMAN DRINKING WATER CRITERIA FOR DIMP CALCULATED FROM DATA ON THREE ANIMAL SPECIES

Animal	Criterion (mg/L)
Dog	26.3
Rat	52.5
Mouse	88.2

Considering the most sensitive species and an uncertainty factor of 100, the recommended drinking water criterion for humans is that derived from experiments on dogs, i.e. 26.3 mg/L.

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APPENDIX A

Eye Irritation and Skin Sensitization Studies Using Diisopropyl Methylphosphonate (DIMP)

HSHB-MO-T (DASG-PSP-E/22 Aug 86) 1st End Mr. Weeks/av/AUTOVONG 584-3980
SUBJECT: Eye Irritation and Skin Sensitization Studies Using Diisopropyl Methyl Phosphonate (DIMP)

USAEHA, Aberdeen Proving Ground, MD 21010-5422 5 FEB 1987

TO: HQDA(DASG-PSP-E), 5111 Leesburg Pike, Falls Church, VA 22041-3258

1. Requested animal studies with DIMP have been completed at this Agency.

2. Results of rabbit eye irritation studies conducted by the method of Draize show that technical grade DIMP produces moderate corneal opacity lasting seven days. No iritis was seen but DIMP caused conjunctiva irritation with moderate to severe redness, chemosis and discharge. In addition, irrigating the eyes with water for one minute, 20 seconds after application of technical grade DIMP did not alleviate the corneal or irritation responses. A 10 percent aqueous suspension of DIMP produced no acute rabbit eye irritation of the cornea or conjunctiva.

3. A guinea pig sensitization study with technical grade DIMP was conducted using the method of Buehler. The test material did not induce a delayed contact hypersensitivity reaction in guinea pigs.

4. Studies are in progress to determine the potential of DIMP for producing sensitization in humans. These studies are scheduled to be completed by 16 March 1987.

FOR THE COMMANDER:

ORIGINAL SIGNED

N. JOE THOMPSON
Colonel, MC
Director, Occupational and
Environmental Health

APPENDIX B

Modified Draize Skin Sensitization Study

MODIFIED DRAIZE SKIN SENSITIZATION STUDY

STUDY #HIM 87-USA-D 1

USEHA

PURPOSE:	To evaluate for irritation and sensitization in a repeat insult patch test on human subjects, the test materials listed below. The method is that of Draize.
TEST MATERIALS:	Test and control articles, as indicated, are furnished by the sponsor. They are identified: DIMP (di isopropyl methyl phosphonate) The sponsor assumes responsibility for any necessary evaluations for purity, strength, and stability.
STORAGE CONDITIONS:	Room Temperature (68-72° F)
PREPARATION FOR DOSING:	10% in water (shake well before using)
SPONSOR:	United States Army Environmental Health Agency Edgewood Arsenal Aberdeen Proving Ground, MD 21010
TESTING FACILITY:	Howard I. Maibach, M.D. San Francisco, CA 9 143
PROPOSED STARTING DATE:	2-17-87
COMPLETION DATE:	3-27-87
SUBJECTS:	215 adult subjects (over 18 years of age) who, prior to commencement of the study, were examined and deemed to be free of any active skin pathology. Medical histories and consent forms were obtained from all subjects.
STUDY MONITOR:	Maurice Weeks
METHODS:	The study was performed by modification of the procedure set forth by Draize.* The test patches were moistened with approximately 0.2 gm of the test material and adequately secured to the skin by means of occlusive bandage (Blenderm tape). The pad is Webril.

MODIFIED DRAIZE SKIN SENSITIZATION STUDY
continued. . .p.2

Patches of the test materials were applied to the upper arms or backs of all panelists. The samples were applied to the patches shortly before application to the panelists' skin.

The study was performed in approximately a six-week period for each subject. During the first three weeks, or the induction period, patches were applied thrice weekly for 48-72 hours. The panelists were instructed to leave the patches on and keep them dry following each application.

All applications of samples were made to the same site.

Approximately two weeks after the sensitization phase, the challenge or elicitation applications were made. The patch was applied to a previously unpatched site. The challenge patches were removed 72 hours following applications. Reactions to the challenge applications were scored at 96 hours following applications.

The scoring scale employed for all evaluations was as follows:

G = minimal glazing, such as in the "peau d'orange"

0 = negative

$\pm$ = equivocal reaction

1 = erythema

2 = erythema and induration

3 = erythema, induration and vesicles

4 = erythema, induration and bullae

MODIFIED DRAIZE SKIN SENSITIZATION STUDY
continued. . . p.3

REPORT:	The report includes incidence and severity of sensitization.
NOTE:	This study was run according to the anticipated principals of GCP.
DATA RETENTION:	The raw data and the original of the final report will be on file at the laboratory for not less than two years. Unused test articles will be returned to sponsor unless otherwise requested.
REFERENCE:	*Marzulli, F. and Maibach, H. CONTACT ALLERGY: PREDICTIVE TESTING IN HUMANS. Advances in Modern Toxicology 4:353-372,1977.
RESULTS:	These are attached. *
COMMENT:	There was no evidence of the elicitation of pre-existing allergic contact dermatitis, or the induction of allergic contact dermatitis. There were no drop outs for toxicity related reasons.

		5-20-87
Date of Sponsor Approval	Study Director	DATE

* THE DETAILED RESULTS AND EVALUATIONS OF EACH OF THE HUMAN SUBJECTS ARE AVAILABLE ON REQUEST FROM USABPDL (SGRD-UBG-O).

APPENDIX C

Details of Methodology Used for Calculation of Criteria

APPENDIX C

DETAILS OF METHODOLOGY USED FOR CALCULATION OF CRITERIA

The methodology used is that established by EPA and published in the Federal Register.[1,2]

1. No-observable effect level (NOEL) calculation for animals

$$\text{NOEL} = \frac{\text{No-effect dietary concentration of test compounds (mg/kg)} \times \text{Daily food or water intake (kg)}}{\text{Body weight of test animal (kg)}}$$

The daily food or water intake and the average body weight of the test animals is taken from the Registry of Toxic Effects of Substances.[3]

2. Derivation of the Acceptable Daily Intake (ADI) in mg/kg/day

$$\text{ADI} = \text{NOEL}/100$$

The NOEL is converted into an ADI for man by dividing by an uncertainty factor of 100. The guidelines for using the uncertainty factors are given in References 4-6, and Appendix D.

3. Calculation of the drinking water criteria, C

$$C = \frac{\text{ADI} \times 70}{2}$$

Calculations of criteria are made using the standard exposure assumptions[2] of 2 liters of water and an average body weight of 70 kg for man.

REFERENCES

1. Environmental Protection Agency. 1979. Water Quality Criteria. Request for Comments. Fed. Reg. 44(52):15926-15981.

2. Environmental Protection Agency. 1980. Water Quality Criteria Documents; Availiability. Fed Reg. 45(231):79318-79379.

3. Registry of Toxic Effects of Chemical Substances 1983-1984 Supplement. 1985. Ed. by R.L. Lewis and D.V. Sweet, Vol 1, A-G, p. xxxv (Table II). NIOSH, Cincinnati, OH (DHHS, (NIOSH) Publication No. 86-103).

4. Vettorazzi, G. 1976. Safety Factors and Their Application in the Toxiclogical Evaluation, in The Evaluation of Toxicological Data for the Protection of Public Health. Ed. by W.J. Hunter and J.G.P.M. Smeets. Pergamon Press, Oxford, New York. pp. 207-223.

5. Drinking Water and Health. 1977. Safe Drinking Water Comittee, Advisory Center on Toxicology, N.R.C./N.A.S., Washington, DC. pp. 803-804.

6. Drinking Water and Health. Volume 5. 1983. Safe Drinking Water Commmittee, Board on Toxicology and Environmental Health Hazards, N.R.C./N.A.S., Washington, DC. p.2.

APPENDIX D

Teleconference call on 19 August 1986
(National Research Council, Committee on Toxicology)

NATIONAL RESEARCH COUNCIL

BOARD ON ENVIRONMENTAL STUDIES
AND TOXICOLOGY

2101 Constitution Avenue Washington, D.C. 20418

COMMITTEE ON TOXICOLOGY
(202) 334-2616

August 25, 1986

MEMORANDUM

TO: The Record

FROM: Francis N. Marzulli

SUBJECT: Teleconference call on 19 August 1986

A telephone conference call was conducted on 19 August 1986 by the NRC/Committee on Toxicology at the request of the Department of Army Surgeon General, Preventive Medicine Division. The following personnel participated at indicated addresses:

Joseph Henry Bldg, Rm 454

Jack C. Dacre, USAMBRDL, Ft. Detrick, MD
David Rosenblatt, USAMBRDL, Ft. Detrick, MD
Hugh C. McAlear, HQDA (DASG PSP), Falls Church, VA
Joel C. Gaydos, HQDA (DASG PSP), Falls Church, VA
F. N. Marzulli, NAS/NRC, COT Senior Project Officer, BEST
K. S. Bakshi, NAS/NRC, COT Staff Officer, BEST

Roger O. McClellan, Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM, COT chairman
Carol Angle, Univ. of Nebraska, Med. Schl., Omaha, COT
David W. Gaylor, Rockville, MD (temporary address), COT
William Halperin, Loveladies, NJ (temporary address), COT
Rogene F. Henderson, Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM, COT
Marvin A. Schneiderman, Mt. Desert, ME (temporary address), COT Senior Staff Officer, BEST
Richard Thomas, Baltimore, MD (temporary address), NAS/NRC, Director Toxicology and Epidemiology Division, BEST

SUMMARY

The NRC Committee on Toxicology (COT) was asked by the U.S. Department of Army to review Technical Reports 8302 and 8610 in order to discuss (via telephone conference on 19 August 198[illegible] appropriate extrapolation procedures and safety factor that should be used in recommending a water standard for diisopropyl methylphosphonate (DIMP).

The COT concluded that it was appropriate to use a safety factor of 100 (rather than 1,000) starting with the NOEL for the most sensitive species (dog) and using body weight, rather than surface area, as a basis for estimating limits for DIMP in drinking water. On this basis, the recommended limit is 26.3 mg/l (26.3 ppm). The use of body weight rather than surface area is consistent with EPA usage for establishing drinking water standards.

It was suggested that Tech. Report 8610 provide tables that include numbers of animals and additional details, such as experimental design. Dosage units for acute and chronic studies should enable easy comparison (i.e., both mg/kg in diet and mg/kg body weight should be used where appropriate; acute LD_{50}'s should be reported in both units).

When information is available from 90-day studies, safety factors of either 100 or 1,000 may be needed depending on the amount of toxicity information available. It was suggested that reference be made to safety factors used in NRC reports beginning with "Drinking Water and Health, Vol. 1," and, most recently, Vol. 6, in order to support a safety factor of 100 for DIMP. The EPA Office of Pesticides would normally use a safety factor of 1,000 when no long-term carcinogenicity studies are available, however, the Safe Drinking Water Committee may use either 100 or 1,000 depending on the amount and quality of data. The information that supports a 100-fold safety factor includes:

1. Negative findings in 90-day rat, mouse, and dog feeding studies at doses tested (including lack of blood and brain anticholinesterase activity in rats and negative histopathology of nervous system in 3 species).

2. Lack of mutagenicity in Ames test and in yeast.

3. Lack of developmental toxicity in rats.

4. Lack of toxicity in rat reproduction study.

5. Lack of effects in a neurotoxicity study in chickens.

Dimethyl methylphosphonate (DMMP), a compound that is chemically related to DIMP, was reported by NIH in a 2-yr bioassay study to produce "some evidence of carcinogenicity" in male rats. The effect seen in male rats is due to hyaline droplet-type nephropathy, a metabolic process involving the formation of a complex between chemical and protein that is species-specific for the male rat and does not occur in humans. Furthermore, DIMP is unlikely to produce this type nephropathy on a structure-activity basis.

During the aftermath of the conference call, Marzulli and Bakshi continued to discuss other aspects of the DIMP report that had not been addressed (with the Army representatives at the Joseph Henry Bldg.). It was suggested that the ocular irritation test be redone using 10% DIMP in rabbit eyes, to clarify findings reported in Tech. Report 8302. It was also suggested that a more sensitive guinea pig test for skin sensitization than the Draize procedure be employed (such as one using Freund's Complete Adjuvant). Alternatively, skin sensitization could be tested on humans using a 10% aqueous solution.

A tape recording was made of this conference call that is retained in files of the COT.

It is suggested that Tech. Report 8610 be submitted to COT for final review when adjustments suggested at this meeting have been accomplished.

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2	Office of the Surgeon General, US Army ATTN: DASG-PSP-E 5111 Leesburg Pike Falls Church, VA 22041-3258

END

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