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Office of Toxic Substances
Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Attn: 8(e) Coordinator

Re: 2-Isocyanatoethyl Methacrylate
CAP Agreement No. CAP-0111
Reference No. CAP00746

Dear Sir/Madam:

submits the enclosed document titled:

ACUTE INHALATION STUDIES OF 2-ISOCYANATOETHYL METHACRYLATE (IEM)

pursuant to TSCA Section 8(e) Compliance Audit Program.

The document contains information which may reasonably support the conclusion that the referenced chemical may present a substantial risk of injury to human health or the environment, as indicated in the Reporting Guide provided by EPA in connection with the CAP.

has not, however, determined that any risk actually exists. The information is summarized below:

EXPOSURES OF RATS TO IEM VAPORS FOR 6 HOURS AT CONCENTRATIONS OF 2, 4, AND 7 PPM SHOWED THAT LC50 FOR A 6-HOUR EXPOSURE FOR MALE RATS IS 4.4 PPM, FOR FEMALE RATS 5.3 PPM. EXPOSURES OF RATS TO IEM VAPORS FOR 1 HOUR AT CONCENTRATIONS OF 10, 20, AND 40 PPM SHOWED THAT LC50 FOR A 1-HOUR EXPOSURE FOR MALE RATS IS 24.2 PPM, FOR FEMALE RATS ~35 PPM. THE CAUSE OF DEATH WAS STRONG IRRITATION TO THE RESPIRATORY TRACT CAUSING SEVERE RESPIRATORY DIFFICULTIES WHICH LED TO DEATH FROM 1 TO 12 DAYS AFTER THE EXPOSURE.

requests guidance from EPA whether the Agency believes the information contained in this document satisfies the criteria in the CAP Reporting Guide. Any correspondence relating to this submission should reference document number CAP000746.

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Where appropriate, three types of information have been removed from the document: the term " Confidential"; individual employee/researcher names (due to privacy considerations); and internal number systems. This is done with prior agreement from EPA. The original documents containing this information are retained according to a document retention policy.

Sincerely,

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Enclosures

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ACUTE INHALATION STUDIES OF 2-ISOCYANATOETHYL
METHACRYLATE (IEM)

By:

SUMMARY

Exposures of rats to IEM vapors for 6 hours at concentrations of 2, 4, and 7 ppm showed that LC_{50} for a 6-hour exposure for male rats is 4.4 ppm, for female rats 5.3 ppm. Exposures of rats to IEM vapors for 1 hour at concentrations of 10, 20, and 40 ppm showed that LC_{50} for a 1-hour exposure for male rats is 24.2 ppm, for female rats 35 ppm. The cause of death was strong irritation to the respiratory tract causing severe respiratory difficulties which lead to death from 1 to 12 days after the exposure.

INTRODUCTION

IEM (2-isocyanatoethyl methacrylate) is a potential new now being produced in experimental quantities. The use of this chemical in coating materials will be restricted to industry for the foreseeable future. The inhalation toxicity of this material is not known; by comparison to other materials containing $-N=C=O$ groups (especially toluene diisocyanate) the material can be presumed to be toxic at low levels.

Range-finding toxicity data obtained in this laboratory¹ indicate that the material is moderate to low in acute oral toxicity, with an LD_{50} in rats of 670-2000 mg/kg. Contact of the undiluted material with the eyes will cause corneal damage that could lead to permanent impairment of vision. Undiluted material will cause burns of the skin in a short

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time, especially if confined under clothing. IEM does not appear to be absorbed through the skin in acutely toxic amounts, but it has been shown² to cause skin sensitization in guinea pigs. The material was not mutagenic in certain microbial assays.²

The purpose of this study was to determine the concentration range in which LC₅₀ for rats would occur for a 6-hour exposure to IEM vapors in air and also for a 1-hour exposure. Based on the results of this study, further inhalation exposures will be planned.

ANALYTICAL METHODS

The analysis of IEM in air in the low ppm range presents difficulties. Previous work in this laboratory showed that "standard" gas chromatography methods were not satisfactory for use at levels below 10 ppm IEM in air. The problem was presented to

, Analytical Laboratory, who developed a gas chromatography method suitable for this analysis; the details are given in a report by Boyle and Blaser.³ The method described below is based upon their work.

Instrument: Varian 1400

Column: 3% FC-431 on 40/60 mesh chromasorb T, in a glass column 6' x 2 mm I.D. Carrier is "zero" air, at a flow rate of ~60 ml/min. Isothermal at 105°C. Column conditioned with N₂ at 150°C 16 hours, then several days at 110°C with air.

Sample loops: Glass, 2 mm I.D., each having a volume of 3 ml. All connections in the chromatograph are made with 1/16" glass-lined stainless steel tubing. Valve is an 8-port, "zero volume" valve.

Detector: Flame ionization, 225°C. H₂ flow 30 ml/min; air 250 ml/min.

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Standardization was done by injecting 10 μ l of a solution of IEM in CH_2Cl_2 into a 50-liter Teflon-lined polyester plastic bag, using the so-called "U-tube" technique. The concentration of IEM in the CH_2Cl_2 solution was made so that the concentration of IEM in the plastic bag was the same as the intended concentration to be used in each given exposure. Linearity of response of the gas chromatograph was shown to be satisfactory; duplicate injections of standard (once the GC column had stabilized for the range in which it was to be used) gave satisfactory repeatability.

EXPOSURE CHAMBERS AND VAPOR GENERATION

Six-hour Exposures

A 4.3 m^3 Rochester-type inhalation chamber was used for the 6-hour exposures. For each exposure, 10 Fisher 344 rats of each sex and 7-9 weeks old, were placed in a group of four 9" x 9" x 14" cages (5 rats of each sex per cage). The cages were closely grouped in the center of the chamber on the top shelf. The line which sampled chamber air for analysis was placed with its opening in the center of the group of four cages, just at the top of the cages; presumably what was then measured is the concentration of IEM in the air just before it reaches the rats (air flow in the chamber is from top to bottom).

In some preliminary tests, vapor generation by metering liquid IEM into a heated flask appeared to give erratic behavior.* Therefore, the vapor generation method employed consisted of passing air through a perforated plate distillation column (15 plates) while liquid IEM was continuously recirculated from the flask below the column to the top of the column, so that each plate in the column had a small layer

*Because of the difficulties of generating a steady concentration of IEM vapor in air, and the difficulties of analysis of IEM vapor in air, previous inhalation studies on IEM from this laboratory should probably be ignored.

of liquid on it. Each stage of the column, once steady state operation was reached, exhibited a good frothing action, and it was thus assumed that air leaving the column was saturated with IEM. Calculations from vapor pressure data supplied by Thermal Lab showed that, at 23°C, saturated air contains 250 ppm of IEM. Air exiting from the distillation column was immediately diluted into the main air flow into the chamber, at a dilution factor appropriate for the given exposure. It was found that the analytical concentration of IEM in the chamber for each exposure was only about 1/2 the calculated amount. Therefore, during the 6-hour exposures, analysis of chamber air was made at least once every half hour, and as often as every 3 minutes during start-up. Any deviations from target concentration were corrected as soon as possible by appropriate adjustment of the air flowing through the distillation column.

Three 6-hour exposures were done at target concentrations of 7, 4 and 2 ppm of IEM in air. The calculated time-weighted averages based on analysis were 6.82 ppm, 3.96 ppm, and 2.03.

1-hour Exposures

These exposures, done at considerably higher concentrations, were done in a small 150-liter Rochester-type inhalation chamber; the vapor generating apparatus described above does not have sufficient capacity to supply IEM vapors at concentrations as high as 40 ppm to a chamber as large as 1 m³ or greater. Because of the much smaller volume of the chamber employed, it was necessary to do each exposure to a given target concentration twice: the first exposure using 10 male rats, the second exposure using 10 female rats. For each exposure, 10 Fisher

344 rats 7-9 weeks old were placed in two 9" x 9" x 14" cages (5 rats per cage). The two cages were placed on the top shelf of the exposure chamber. The line which sampled chamber air for analysis was placed with its opening between the 2 cages, just at the top of the cages; presumably what was then measured is the concentration of IEM in the air just before it gets to the rats.

Vapor generation was done precisely as described above for the 6-hour exposures, except that the air dilution factor was, of course, much smaller so that the required concentrations could be reached. During these one-hour exposures, analyses were made every 2 minutes throughout each exposure; adjustments were made in air flow rates as required to hold the vapor concentrations as steady as possible at or near target concentrations for the duration of each exposure.

Six one-hour exposures were done, 2 (males and females) each at target concentrations of 40, 20, and 10 ppm of IEM in air. The measured concentrations and standard deviations were: 36.32±2.48 ppm (males), 36.57±1.67ppm (females); 20.39±.78 ppm (males), 19.77±1.09 ppm (females); 9.74±.56 ppm (males); 9.71±.42 ppm (females).

ANIMALS

The animals were Fisher 344 rats, 7-9 weeks old. Each exposure group and the control group consisted of 10 rats of each sex. Animals were weighed just prior to exposure, and approximately 3 times/week thereafter. Surviving animals were maintained in the laboratory for 2 weeks after exposure, and then were submitted to necropsy. Any rat dying post exposure (none died during any exposure) was promptly submitted to necropsy. Necropsy consisted of gross pathological examination, but no histologic examinations were made.

RESULTS

6-hour Exposures

Exposure to 7 ppm IEM (6 hours): During exposure, all rats showed progressively increased signs of eye and nasal irritation and respiratory difficulties. Just after exposure there were signs of eye irritation, and dried dark red-brown exudate on the noses; respiratory difficulties appeared to have diminished, only slight rales being observable in a few rats. However, 16 hours later there was evidence of severe respiratory distress in all animals exposed. Of the 10 male rats exposed, 2 died between 24 and 32 hours post exposure, 4 died between 32 and 48 hours post-exposure. A seventh rat was found to be clearly moribund 72 hours post-exposure, and was sacrificed and necropsied. The remaining 3 rats survived 14 days until sacrifice and necropsy, but all showed severe and monotonous weight loss until sacrifice. Of the 10 female rats so exposed, 4 died between 24 and 32 hours post-exposure, 3 more by 48 hours post-exposure. The remaining 3 rats survived 14 days until sacrifice; one of these showed essentially monotonous weight loss, but the other two, after severe weight loss, eventually began to gain weight and reached normal weight levels.

Exposure to 4 ppm IEM (6 hours): Signs in the rats during and post-exposure were essentially the same as in the 7 ppm exposure, but slightly less pronounced. Of the 10 male rats exposed, 6 died between 32 and 48 hours post-exposure. The survivors showed essentially monotonous weight loss until sacrifice 14 days later, but appeared to be stabilizing at that time, with 2 rats showing weight gains just prior to sacrifice. Of the 10 female rats so exposed, 3 died between 24 and 32 hours post-exposure, the rest surviving until sacrifice. After

severe initial weight loss, 6 of the 7 survivors re-gained weight and were at normal levels at sacrifice, but the seventh showed essentially monotonous weight loss to sacrifice.

Exposure to 2 ppm IEM (6 hours): Signs in the rats during exposure were slight, and just after the 1/2-hour venting period post-exposure they appeared normal. None of the rats, either male or female, died post-exposure up to sacrifice 14 days later. All suffered a severe initial weight loss (more severe in the males than the females), but then began to gain weight and had reached normal levels by sacrifice.

LC₅₀ calculations⁵ gave the following results:

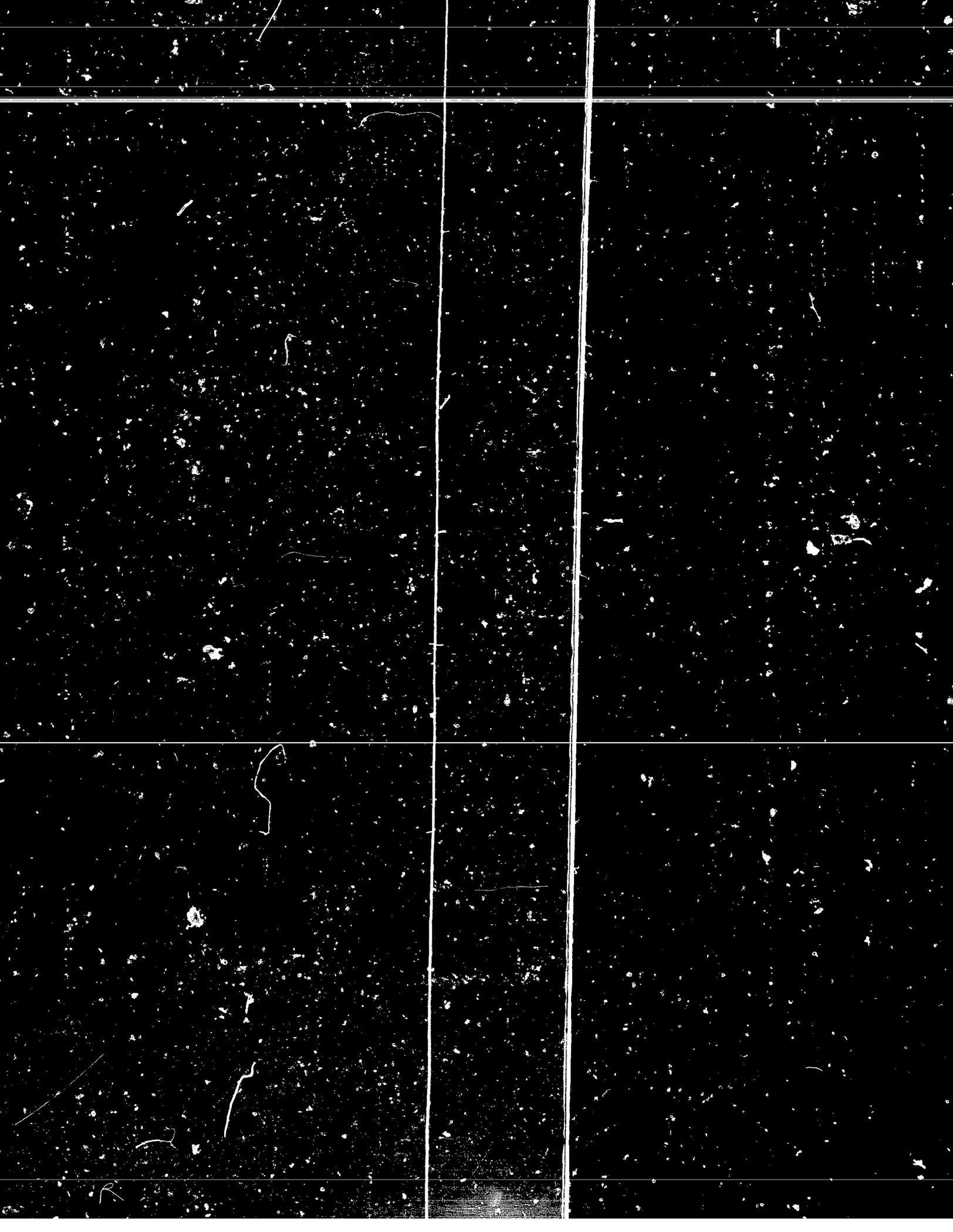
Males (6-hour exposure) LC₅₀ = 4.44 ppm (95% CL 3.21-6.53) -

Females (6-hour exposure) LC₅₀ = 5.27 ppm (95% CL 3.98-7.99) -

1-hour Exposures

Exposure to 40 ppm IEM (1 hour): Signs in the animals developed much more quickly than in the 6-hour exposures. During exposure, all rats showed signs of eye and nasal irritation and respiratory difficulties. After exposure and a 30-minute venting period, both the male and female rats, when removed from the chamber, showed diminished signs of respiratory difficulties, but did show labored breathing, stains on their noses, and appeared lethargic.

Of the 10 male rats exposed, 2 died within 24 hours post-exposure, 2 more died within 100 hours post-exposure. The six male survivors to this point, after having shown severe initial weight losses, appeared to be stabilized in weight at 1 week post-exposure, but shortly thereafter lost weight rapidly and steadily, with 4 more dying in the 11th to 13th day post-exposure. The two rats surviving to necropsy at 14 days post-exposure continued to lose weight, showed labored breathing, and were extremely lethargic.



Of the 10 female rats exposed, 2 died 4 days post-exposure, 3 more died in the 11th and 12th days post-exposure. The five survivors appeared to have stabilized in weight prior to necropsy, and did not show abnormal signs.

Exposure to 20 ppm IEM (1 hour): Signs during and post-exposure were similar to those seen in rats exposed to 40 ppm IEM, but to lesser extent. The females apparently tolerated the exposure better than the males. The 10 males exposed showed severe weight losses, then appeared to stabilize at about 7 days post-exposure, but then 9 of the 10 lost weight rapidly, and four of these died on the 10th and 11th days post-exposure. Five of the six survivors continued to lose weight rapidly throughout the 14-day post-exposure period, showed labored breathing and extreme lethargy; the sixth, however, was gaining weight and appeared normal. The 10 females showed severe temporary weight losses, but 4-5 days post-exposure their weights stabilized, and at the end of 14 days all their weights were near normal and all had a normal appearance.

Exposure to 10 ppm IEM (1 hour): Signs during exposure were slight; females showed no signs post-exposure, and males showed no signs except for slight stains on the noses of a few. All the males and most of the females showed weight losses post-exposure, but in only one male and one female was the loss severe, and all rats of both sexes were gaining weight and apparently in normal condition 14-days post-exposure.

LC₅₀ calculations⁵ gave the following results:

males (1-hour exposure) LC₅₀ = 2.42 ppm (95% CL 17.8-33.4)

females (1-hour exposure) LC₅₀ 36 ppm (insufficient data
for statistical treatment)

Observations on mortality and weight changes for both the 6-hour and 1-hour exposures are summarized in Table 1.

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PATHOLOGY

Six-hour Exposures

Rats Exposed to 2 ppm IEM Vapor

All male and female rats exposed to 2 ppm IEM vapor survived the 14-day post-exposure observation period. Gross pathologic examination revealed no grossly visible lesions in any of the male rats. Examination of the female rats in this group revealed focal pneumonia in the lungs of 5/10 and focal atelectasis (collapse) in the lungs of 1/10. These minimal lesions in the lungs of the female rats were considered to be due to exposure to vapors of IEM since similar lesions of the lungs are observed only in aged rats of this age.

Rats Exposed to 4 ppm IEM Vapor

Of the rats exposed to 4 ppm IEM vapor 6/10 males and 3/10 females died within 48 hours after exposure. In general the rats that died had porphyrin-containing secretions on the facial regions adjacent to the eyes, nose and/or mouth. This was considered to be an indication of irritation of the ocular and nasal mucous membranes. Corneal or conjunctival alterations indicative of eye irritation were observed in 4/6 males but not in the females that died. Examination of the internal organs and tissues of the rats that died revealed variable evidence of upper respiratory irritation such as inflammation of the nasal mucosa (rhinitis), and excess quantities of gaseous material in the gastrointestinal tract. Congestion of the lungs which was observed in some rats may have been indicative of an effect on this organ. Congestion of the liver and kidneys which was observed in rats that died was considered to be an agonal event and not a primary effect of treatment.

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All male rats killed at the end of the 14-day observation period had patchy areas of pneumonia usually accompanied by inflammatory exudate in the trachea and/or bronchi; decreased quantities of ingesta within the gastrointestinal tract; decreased deposits of adipose tissue, and a shrunken, atrophic appearance of the thymus. In the surviving female rats 2/7 had focal pneumonia; 4/7 had decreased deposits of adipose tissue, and 1/7 had a shrunken, atrophic thymus. The focal pneumonia observed in the surviving rats was considered to be indicative of probable irritation to the lungs whereas the observations of decreased deposits of adipose tissue and thymic atrophy were interpreted to be secondary effects related to stress incurred as a result of primary effects of the test material on the respiratory system.

Rats Exposed to 7 ppm IEM Vapor

Seven of 10 male and 7/10 female rats exposed to 7 ppm IEM vapor died or were killed in a moribund condition within 72 hours post-exposure. Of these all but one male died within 48 hours post-exposure. Most males and females that died had accumulations of prophyrin-containing secretions on the facial region (eyes, nose and/or mouth); decreased ingesta and/or increased quantities of gaseous material in the gastrointestinal tract; congestion of the liver and kidneys, and several had alterations of the cornea and/or conjunctiva. Of rats that survived the 14-day post-exposure observation period: 3/3 males and 1/3 females had focal pneumonia and thymic atrophy, and 3/3 males and 2/3 females had decreased deposits of adipose tissue. Thus, the lesions in the rats exposed to 7 ppm IEM were similar to those described above for rats

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exposed to 7 ppm IEM. The toxicological significance of these lesions was also similar to that discussed above for rats exposed to 4 ppm IEM vapor. A variety of other pathological alterations were observed in only a small number of rats within an exposure group. These alterations were either considered to be spontaneous in nature and unrelated to treatment or were not considered to be critical in characterization of the toxicological response in these rats and thus were not discussed individually.

One-hour Exposures

Rats Exposed to 10 ppm IEM Vapor

Four male and 4 female rats from the group exposed to 10 ppm IEM were examined at the end of the 14-day observation and had no lesions that could be attributed to treatment with the test material.

Rats Exposed to 20 ppm IEM Vapor

Ten male and 3 female rats from the group exposed to 20 ppm IEM were subjected to gross pathologic examination. Focal cloudiness of the cornea of one eye was the only grossly visible lesions observed in the female rats that was considered to be possibly related to treatment. Four of 10 male rats in this group died during the 14-day observation period. These deaths were considered to be due to treatment with the test material. In general, the males in this group, whether submitted dead or alive, had lesions of the respiratory system, i.e., congestion of the nasal mucosa, focal pneumonia and failure of the lungs to collapse normally upon opening the trachea and bronchi that were considered to be primary effects of treatment with the test material.

Cloudiness or opacity of the cornea of one or both eyes was observed in 4/10 males and was also considered to be a treatment-related effect. In addition, decreased deposits of adipose tissue and/or dehydration of the tissues were observed in most of the males. These were considered to be secondary effects incurred as a result of the failure of the rats to consume normal quantities of food and water which, in turn, can be attributed to the pneumonia observed in these rats.

Rats Exposed to 40 ppm IEM Vapor

Eight male and 5 female rats in this group died during the 14-day observation period. These deaths were considered to be due to treatment with the test material. Gross pathologic examination of all 10 male and 10 female rats in this group revealed a variety of grossly visible lesions that were indicative of irritation of the upper and lower respiratory passages. Lesions observed that were considered to be indicative of respiratory irritation were as follows: exudative material around the external nares in 8/10 males and 4/10 females; congestion of the nasal turbinate mucosa in 7/10 males and 2/10 females; inflammatory exudate in the nasal passageways of 6/10 males and 2/10 females; focal pneumonia in 6/10 males and 3/10 females; failure of the lungs to collapse normally upon opening trachea and bronchi in 3/10 males and 3/10 females; areas of congestion and edema of the lungs in 1/10 males; diffuse congestion of the lungs with focal atelectasis in 1/10 females, and distention of the stomach with air which is indicative of upper respiratory obstruction in 5/10 males and 2/10 females. Cloudiness of the cornea of one or both eyes was observed in 2/10 males

which was considered to be a probable effect of treatment. A variety of other pathologic alterations such as dehydration, decreased deposits of adipose tissue, thymic atrophy, congestion of the abdominal viscera or liver, and a roughened appearance of the haircoat were observed which were considered to be secondary effects that were incurred as a result of inflammatory lesions of the respiratory system.

CONCLUSIONS

Mortality and weight data are summarized in Table 1. Clearly, all the adverse effects seen are dose-related, and appear to be somewhat more severe in the male rats than in the female rats (such difference between ability of the sexes to tolerate toxic insult is common).

As a result of these studies, it is reasonable to conclude that the acute inhalation toxicity of 2-isocyanatoethyl methacrylate is roughly similar to that of toluene diisocyanate (TDI). The LC50 for rats* exposed to TDI for 4 hours has been reported⁶ to be 13.9 ± 1.52 ppm. Interpolation between the results for the one-hour and 6-hour exposures to IEM reported herein would estimate the LC50 for exposure of male rats to IEM to be ≈ 7 ppm. The difference between a 4-hour LC50 of 7 ppm (IEM) and of 14 ppm (TDI) is not regarded as significant, particularly because, in the two compared studies, the vapor generation methods were different, analytical methods were not comparable, and different strains of rats were employed.

*Presumably male rats, but the sex and source (strain) of the rats were not stated in the reference quoted.

Table 1

BODY WEIGHT EFFECTS RESULTING FROM ACUTE EXPOSURES
TO 2-ISOCYANATO ETHYL METHACRYLATE

Dose (Nominal)	Males			Females		
	Dead	Severe Weight Loss	Temporary Weight Loss	Dead	Severe Weight Loss	Temporary Weight Loss
1-Hour Exposure						
10 ppm	0/10	1/10	10/10	0/10	1/10	8/10
20 ppm	4/10	9/10	10/10	0/10	7/10	10/10
40 ppm	8/10	10/10	10/10	5/10	10/10	10/10

LC50=24.2 ppm (95% CL 17.8-33.4) LC50 ~36 ppm

6-Hour Exposure

2 ppm	0/10	0/10	10/10	0/10	0/10	8/10
4 ppm	6/10	10/10	10/10	3/10	4/10	10/10
7 ppm	7/10	10/10	10/10	7/10	8/10	10/10

LC50=4.44 ppm (95% CL 3.21-6.53) LC50 = 5.27 ppm (95% CL 3.98-7.99)

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3. , "The determination of 2-isocyanatoethyl methacrylate in air," (1977);
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