TOXIC MECHANISMS OF INHALED METHYL METHACRYLATE VAPOR

TERMINAL REPORT

GRANT:2R01 OH 00518-03, 04

Martin F. Tansy, Ph.D.
Principal Investigator

February 21, 1979

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. Recipient's Accession No. PB88 252668/AS
4. Title and Subtitle Toxic Mechanisms of Inhaled Methyl Methacrylate Vapor			5. Report Date 79/02/21
			6.
7. Author(s) Tansy, M. F.			8. Performing Organization Rept. No.
9. Performing Organization Name and Address Temple University School of Dentistry, Philadelphia, Pennsylvania, Terminal Report			10. Project/Task/Work Unit No.
			11. Contract(C) or Grant(G) No. (C) (G) OH-00518-0, OH-00518-04
12. Sponsoring Organization Name and Address			13. Type of Report & Period Covered
			14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

Experiments were undertaken to investigate the effect of exposure to 116 parts per million (ppm) methyl-methacrylate (80626) for 8 hours/day, 5 days/week for 3 months on mature male Sprague-Dawley-rats. Results supported the earlier findings that long term methyl-methacrylate inhalation influences blood chemistry. Earlier findings of depressed body weight, epididymal and popliteal fat pad weight reduction were not confirmed. No effect on various gross metabolic parameters was demonstrated. There appeared to be a relationship between systematic methyl-methacrylate vapor exposure and gastrointestinal motor performance. Chronic exposures were associated with frank damage to tracheal epithelial cells, including denudation of microvilli. Frank liver damage also resulted. The median lethal dose was found to be 7093 parts per million. No differences were noted in glucose absorption in exposed versus control animals. Preliminary studies were also performed to determine whether or not exposure of rats to less than the median lethal dose levels of ethyl-acrylate (140885) (250ppm) or butyl-acrylate (141322) (100ppm) could produce significant effects on the motor activities of the stomach. A prompt decrease in gastric motor activity resulted from these exposures. The extent of the reduction in contractility of the small intestine was far more pronounced with ethyl-acrylate and butyl-acrylate than it was with methyl-methacrylate.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms

NIOSH-Publication, NIOSH-Grant, Grant-Number-OH-00518-03, Grant-Number-OH-00518-04, Age-factors, Laboratory-animals, Resins, Gastrointestinal-system-disorders, Inhalation-studies, Chronic-exposure, Inhalation-studies

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 7
	20. Security Class (This Page)	22. Price A02/MF A01 6.95

TERMINAL REPORT

GRANT NUMBER - 2R01 0H00518-03,04

PERIOD COVERED - 1977-79

PRINCIPAL INVESTIGATOR - Martin F. Tansy, Ph.D.

INSTITUTION - Temple University School of Dentistry

PROJECT TITLE - Toxic Mechanisms of Inhaled Methyl Methacrylate Vapor

Specific Aims. The proposed experiments were designed:

1. To confirm our previous observation that a three month-exposure of young, male, Sprague Dawley rats to a concentration of 116 ppm of methyl methacrylate vapor for 8 hours per day, five days per week, is associated with a significantly lower average body weight and absence of body fat when compared to a sham-exposed population.

2. To repeat the above study under the same conditions utilizing two groups of mature (200-220 gram) rats of the same species. The purpose of this experiment is to determine whether the observed effects can be inferred to be substantially independent of the ages of the populations.

3. To determine the effects upon both daily food intake, daily average body weight, and weekly fecal fat content of a group of young, male, Sprague Dawley rats during a 3-month exposure to 116 ppm of methyl methacrylate monomer vapors as compared to the daily food intake, daily average body weight, and weekly fecal fat content of a similar group of sham exposed rats.

4. To determine average values for intestinal transit and intestinal absorption (using a simultaneous measurement method) of young, male, Sprague Dawley rats exposed for 1.5 months and three months to 116 ppm of methyl methacrylate monomer vapor and compare the average values to corresponding averages obtained from a similar sham exposed group. In each instance, two sets of determinations will be made: The first groups will be tested immediately following the end of the exposure period. The second groups will be studied the following morning when exposure would normally commence. The prospective purpose of these experiments is to determine the degree of short-term recovery of intestinal motor and absorptive activity after differing periods of exposure and consequent ageing.

5. To determine the effects of 3-month exposure to 116 ppm of methyl methacrylate monomer vapor upon fat metabolism in a population of young, male, Sprague Dawley rats as compared to average parameters for an identical group of sham exposed rats. The parameters of interest are weekly plasma concentrations of lipids (triglyceride, free and esterified

cholesterol and phospholipid), glucose, and gamma glutamyl transpeptidase and the concentration of liver, popliteal fat pad, and epididymal fat pad lipid content and adipocyte glucose oxidative and lipogenic metabolism at the conclusion of the exposure period.

As evidenced by the data of the following communications,

1. Chronic Effects of Methyl Methacrylate Vapor: Observations in Mature Rats. F.J. Hohenleitner and M.F. Tansy. Proceedings 56th General Meeting International Association for Dental Research, 57:289, 1978 (abstract).

2. Chronic Effects of Methyl Methacrylate Vapor: Metabolic Observations in Young Rats. F.J. Hohenleitner and M.F. Tansy. Federation Proceedings, 37:247, 1978 (abstract).

3. Effects of Chronic Methyl Methacrylate (MMA) Inhalation on Ciliary Function. R. Oberly, L.M. Salkin, W.E. Landin, and M.F. Tansy. Proceedings 56th General Meeting International Association for Dental Research, 57:289, 1978 (abstract).

4. LC50 Value for Rats Acutely Exposed to Methyl Methacrylate Monomer Vapor. M.F. Tansy, W.E. Landin, and F.M. Kendall. Proceedings 57th General Meeting International Association for Dental Research, 58:207, 1979 (abstract).

5. Hepatic Function in Mice Chronically Exposed to Methyl Methacrylate Vapor. M.F. Tansy, W.E. Landin, F.M. Kendall, and D.K. White. Proceedings 57th General Meeting International Association for Dental Research, 58:207, 1979 (abstract).

6. Gastrointestinal Motor Inhibition Associated with Acute Exposure to Acrylate Vapors. M.F. Tansy, W.E. Landin, and H. W. Perrong. Gastroenterology (abstract submitted).

7. Chronic Biological Effects of Methyl Methacrylate Vapor II. Body and Tissue Weights, Blood Chemistries, and Gross Metabolic Behavior in the Rat. M.F. Tansy, F.J. Hohenleitner, W.E. Landin, and F.M. Kendall. Environmental Research (paper submitted).

8. Chronic Biological Effects of Methyl Methacrylate Vapor III. Histopathology, Blood Chemistries, and Hepatic and Ciliary Function in the Rat. M.F. Tansy, F.J. Hohenleitner, D.K. White, R. Oberly, W.E. Landin, and F.M. Kendall. Environmental Research (paper submitted).

it was demonstrated that:

1. These studies support the earlier conclusion (Tansy et al., Environ. Res. 11:66, 1976) that long-term methyl methacrylate inhalation can influence blood chemistry (See 7 and 8 above).

2. The previously reported depression of body weight, epididymal and popliteal fat pad weights were not confirmed (see 7).

3. Chronic inhalation exposure of rats to a methyl methacrylate concentration which is close to the accepted TLV is not associated with significant changes in various gross metabolic parameters (See 7).

4. A relationship between systematic methyl methacrylate vapor exposure and gastrointestinal motor performance does in fact exist (See 7).

5. Chronic exposure of rats to 116 ppm of MMA in air might be associated with frank damage to tracheal epithelial cells which included denudation of microvilli. The significance of chronic exposure to MMA upon the function of respiratory ciliated epithelium was studied using grass tree frogs exposed to 116 ppm and 400 ppm of MMA in air by means of measurements of the rate of transport of small glass spheres. No significant effect was demonstrable in the case of frogs which had been subjected to the 116 ppm exposure but transit capability degraded rapidly (with kinetic failure after as few as 5 trials) in those frogs which had been exposed to the higher dosage. Thus, in keeping with its previously reported depressant effect upon active contraction, MMA in concentrations of about 4 times the TLV might exert a definite ciliostatic effect (See 8).

6. Histological observations of sections from the livers of rats chronically exposed to daily concentrations of 116 ppm methyl methacrylate vapor in air for 3- and 6- months indicated the possible presence of frank liver damage in both groups. Despite some evidence of liver damage, the abilities of mice (exposed to either 100 ppm or 400 ppm of methyl methacrylate vapor in air for 160 hours) to metabolize sodium pentobarbital were not impaired (See 8).

7. Under the conditions of our inhalatory experiments the LC50 value for methyl methacrylate was found to be 7093 ppm. Specific recordings from other rats indicated that death during exposure was associated with eventual respiratory failure followed by cardiovascular collapse: These observations are in agreement with those reported in the literature for fatalities produced by methyl methacrylate administration by other routes.

8. Studies on glucose absorption in animals chronically exposed to methyl methacrylate vapor in air did not show any difference between the experimental and sham control groups. Tests of thyroid status using radioimmunoassay T_4 analysis also did not show any difference between the two groups. (in preparation).

One of the goals specified in our summary progress report, dated 21 December, 77 on Grant 0H00518-04 entitled "Toxic Mechanisms of Inhaled Methyl Methacrylate Vapor", was to determine whether the phenomena which we have previously reported for chronic methyl methacrylate exposures constitute common population responses to similar chronic exposures to TLV concentrations of other common, volatile acrylates such as ethyl and butyl acrylate. Pilot experiments were performed to empirically determine whether or not exposure of rats to less than LD_{50} doses of ethyl acrylate or butyl acrylate could produce significant effects on the motor activities of the stomach. The doses of ethyl acrylate and butyl acrylate administered were 250 ppm and 100 ppm respectively. Preliminary observations indicate that the exposure of the rat to these vapors also results in a prompt decrease in gastric motor activity. Although not depicted, intestinal smooth muscle was also affected by ethyl acrylate and butyl acrylate vapor in vitro. In this case tonus was remarkably affected, the observed effect being the eventual reduction of the active force component to zero. Removal of the ethyl acrylate or butyl acrylate vapor source and flushing of the bath did not result in a return of activity to pretreatment levels. The important point to be noted from these results, apart from their general pharmacological significance, is that the extent of the reduction in contractility of the small intestine similar to that seen with methyl methacrylate was far more pronounced with ethyl and butyl acrylate.