ENVIRONMENTAL RESEARCH 11, 66–77 (1976)

Chronic Biological Effects of Methyl Methacrylate Vapor

I. Body and Tissue Weights, Blood Chemistries, and Intestinal Transit in the Rat[1]

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Received July 22, 1975

The effects upon body and tissue weights, various blood parameters, and intestinal transit time associated with chronic exposures of rats to monomeric methyl methacrylate (MMA) vapor concentrations are summarized in this report. The most remarkable and readily apparent phenomenon was the obvious lack of body fat in the group which had been exposed for 3 months to an MMA vapor concentration of 116 ppm in air. It was determined that rats which have received a daily 8-hour exposure to 116 ppm of MMA vapor for 6 months have significantly lower adiposity, as measured by the popliteal fat pad, than those of a similar group which have received sham exposures. It was also determined that protracted exposures to MMA vapor in this concentration were associated with a significant decrease in intestinal transit performance.

Methyl methacrylate monomer polymerizes rapidly and is produced in large quantities as a raw material for the commercial manufacture of acrylic rods, sheets, and tubes. These components can be made with high optical quality and are particularly suitable as shields for outdoor lighting fixtures because of the weather resistance and non-yellowing characteristics of the polymer. Acrylic sheet is used as a glazing material in the construction industry, and methyl methacrylate is also used as a co-monomer to increase the weather resistance of polyester resins.

The weather resistant properties of poly-methacrylates extend to include resistance to degradation by biological tissues and fluids. The monomer can be slowly polymerized and worked into molds or cavities in the form of a dough. As a result it has been estimated that by 1946, 98% of all denture bases were constructed of methyl methacrylate polymers or co-polymers. Surgical uses include the reconstruction of destroyed vertebrae, and as a filler of lytic lesions surrounding internal fixation devices in bone: The polymer achieves a strength equal to that of the surrounding bone.

Dental and medical surgical use of the polymer of methyl methacrylate empirically acknowledges that its tissue toxicity is low. On the other hand, both the liquid monomer and its vapor are considered to be toxic. Inasmuch as most people come

[1] Supported by Public Health Service Research Grant No. OH-00518 from the National Institute of Occupational Safety and Health.

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in contact with the polymer it must be assumed that those at risk would constitute groups occupationally exposed in the course of manufacture, transportation, and eventual use of the monomeric form.

Members of our group became aware of the olfactory properties of the monomer as the result of predictable yearly exposures to an overpowering fetor which emanated from a nearby dental student technique laboratory. Our group has published preliminary evidence that acute exposure to high concentrations of the vapor depresses the *in vivo* spontaneous motor activity of the stomach of the rat and a human (Tansy *et al.*, 1974), inhibits the spontaneous gastrointestinal motor activities of the anesthetized dog (Tansy *et al.*, 1975), and depresses the *in vitro* spontaneous motor activity of intestinal muscle strips of the rat (Tansy *et al.*, 1975).

It was our inferences that the *in vivo* motor effects which we observed were probably due to a direct reversible toxic effect of the gas or a metabolic by-product upon the gastrointestinal neuromuscular complex, and that the delivery of the effective agent to the target sites involved the functions of both the respiratory and cardiovascular systems.

Inasmuch as the acute effects were both toxic and reversible, we decided to determine whether it could be inferred that chronic exposure to a vapor concentration in air, which was close to the maximum permissible occupational exposure concentration, could be associated with significant nontransient differences in the mean values of various functional and metabolic parameters when compared to similar data from a sham population.

MATERIALS AND METHODS

Animals

The target population consisted of 100 male Charles River Sprague–Dawley rats that weighed 90–100 g when received. They were equilibrated for 1 week in closed colony cages (six per cage) and received Purina Laboratory Chow and water *ad libitum*.

Randomization of Animals

Following the equilibration period, the animals were divided into control and experimental populations as follows: One hundred five-digit random numbers were selected from a table and written on file cards along with the selection order numbers. The cards were than shuffled into ascending order according to the five-digit random numbers. The rats were loaded at apparent random into 100 separate containers, labeled from one to 100. The rats were then selected from these containers according to the order number obtained from the shuffled file cards, and numbered by a code from one to 100 in the order that they were selected. The first 50 rats became the control group and the second, the experimental group. At the appropriate times, random samples of equal size were selected from control and experimental groups at the same time. Selection was effected according to the code number of the animal and was randomized as previously described. Inasmuch as the orders of selection were thus determined well in advance, they were maintained in secure conditions during the experiment. The technician who actually selected the animals did so upon notifying another individual of the size of the desired samples and received that number of code numbers for each population. Thus, the initial

segregation and final selection processes may be considered to be reasonably randomized and independent of each other.

Conditions of Exposure

Both control and experimental groups were housed en masse in separate Young and Bertke exposure chambers (Fig. 1). The methyl methacrylate monomer used in this study was purchased from Rohm and Haas Company and c ained 10 ppm of the monoethyl ether of hydroquinone as an inhibitor. Following the first week, MMA vapor was introduced into the experimental chamber for 8 hours per day, 5 days per week, for up to 6 months by means of the apparatus shown in Fig. 2. The calculated gas concentration in the experimental chamber was 135 ppm. One of us (Benhayem), using gas chromatography, estimated the actual concentration in the experimental chamber during steady-state conditions at a peak value of 116 ppm, less than 1 ppm in the room air near the exposure chamber and vaporizer, and an unmeasurably low concentration in the control chamber (Table I). The water supply for both groups was equipped with a standard glass tube which provided a suitably small exposure area in order to minimize the solution of MMA vapor in the water. Samples of food pellets taken during the exposure period were degassed, and the gas and pellets were checked for MMA content which was found to be negligible.

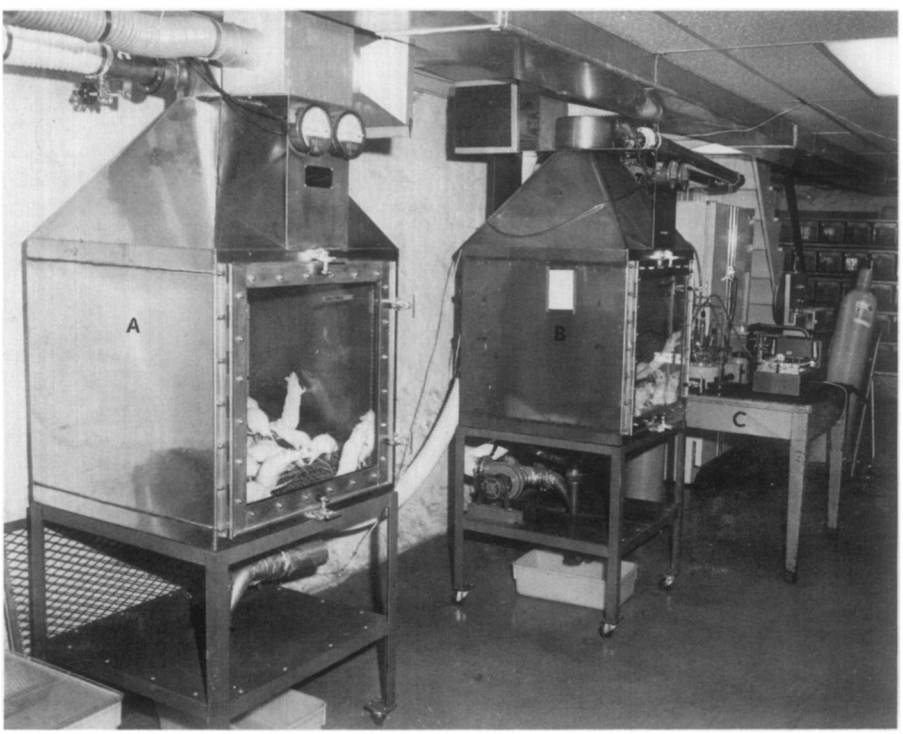

FIG. 1. Dual chamber configuration for long-term exposure and sham exposure of rats to MMA vapor. Chamber A contains the sham population and chamber B the experimental population. During each working day the experimental group received an 8-hour exposure to 116 ppm of MMA vapor produced by gas generator apparatus C.

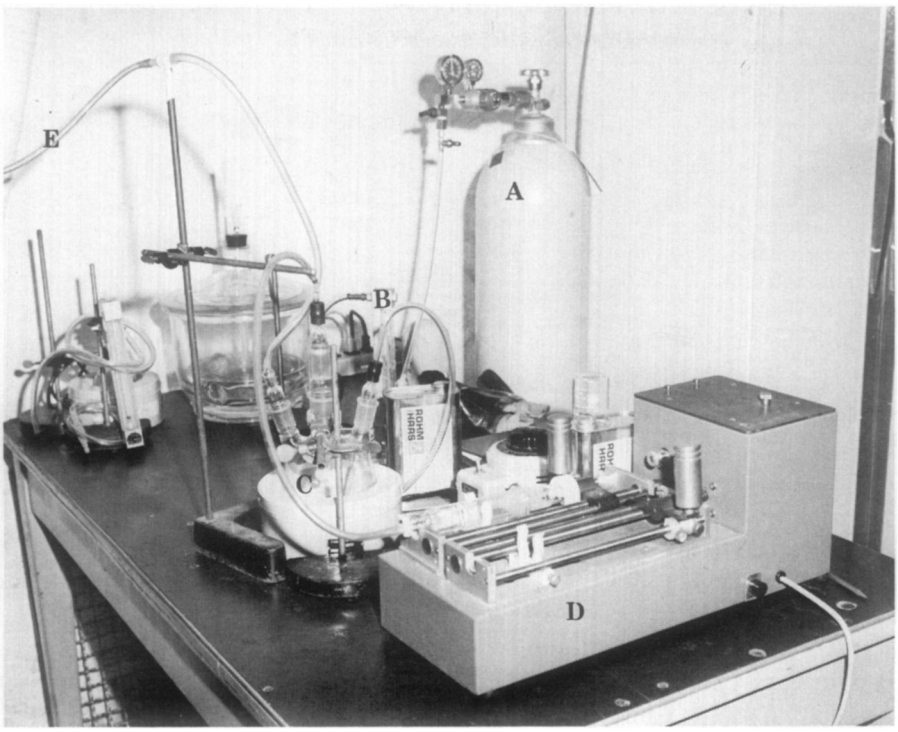

FIG. 2. Gas Generator. Compressed air (A) is fed at a rate measured by rotameter (B) into a vaporization chamber (C) where it is mixed with MMA vapor. Liquid MMA is pumped at a fixed rate from the syringe pump (D) into the vaporization chamber where it vaporizes almost instantaneously. The vapor mixture is conducted by tube (E) into the air supply of the exposure chamber. The measured gas concentration in the exposure chamber was 116 ppm.

An independent measurement of MMA vapor concentration in the exposure chamber was made by Dalaire Consultants, Inc. of Philadelphia, and reported slightly in excess of 100 ppm.

Sequence of the Study

Approximately half of the experimental and half of the sham control animals were removed from the exposure chamber after 3 months and the balance were removed at the end of 6 months. In all cases, the selection of animals, whether for removal or for use in a particular experiment, was conducted randomly in the same manner as, but independently of, the initial randomization and assignment of animal serial numbers. Actual exposure durations were 542 hours for the 3-month group, and 1105 hours for the 6-month group. The experimental protocol for the 3-month study was as follows: Animals were weighed, killed, and blood and tissue samples were obtained promptly. Selected tissues were weighed and blood was used for hematological evaluation by Coulter Counter and SMA 12/60 analysis. The experimental protocol for the 6-month study was as follows: At cessation of exposure, one group of sham controls and one group of exposed rats were segregated for the intestinal transit-time procedure of Macht (as cited by Van Liere *et al.*, 1945). The

TABLE 1
GAS CHROMATOGRAPHIC CONDITIONS

Instrument: Varian Aerograph Model 2440-23782	
Column: 5 ft. × ⅛ inch o.d. stainless steel, packed with 20% carbowax 20 M, coated onto 80–100 mesh Chromasorb W.	
Temperature:	
Column oven (starting)	100°C
Injection port	200°C
Detector	200°C
Gas pressure and flow:	
Helium	68 psi
Helium flow	30 mls/min
Hydrogen	20 psi
Air	20 psi
Attenuation: 32×10^{-11}	
Recorder sensitivity: 1 mV.	
Sample size: 1 ml.	

remaining rats were weighed and promptly killed. Organ weights were obtained and blood was collected for SMA 12/60 analysis. The fat pads from the cauda epididymides and the left popliteal fat pad were removed for weight analysis.

Reduction of Data and Interpretation of Results

Data for each control and experimental group were tabulated. Means and standard deviations were computed and comparisons were made by Student's *t* test under the null hypothesis that the means were equal. The alternate hypothesis was two-tailed: that the means were different. The 5% confidence level for rejection was set in advance.

RESULTS

All animals that were initially received alive survived the experiments. There were no spontaneous deaths in either the sham control or experimental groups. During the entire exposure period it was noted that, during the period of actual exposure, the rats in the exposed group presented a decidedly shaggy appearance when compared to the controls in the adjacent chamber. The exposed animals were not observed to groom themselves when the gas was on. In general, the sham control rats exhibited a better appearance in the morning at the time that gas exposure was scheduled to commence.

Results of the 3-Month Group

At necropsy it was immediately noted that all of the MMA exposed rats exhibited a marked absence of visceral and subcutaneous fat deposits (Figs. 3 and 4). Mean values of body and organ weights are summarized in Table 2. Mean whole body, lung, and spleen weights were significantly lower in the case of the exposed group.

Examinations of mean hematology data (Table 3) and mean SMA 12/60 data (Table 4) indicate that we were able to conclude that the only significant difference which existed between mean parameter values for the 3-month exposed and sham exposed groups was the mean serum alkaline phosphatase concentration of the exposed group, which was significantly elevated.

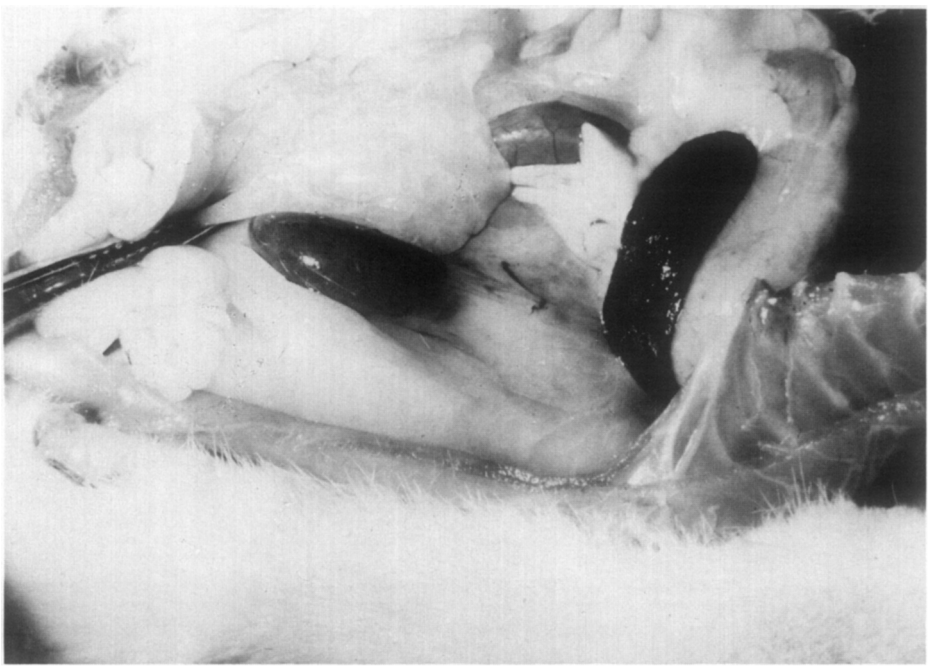

FIG. 3. Autopsy photograph of the appearance of the visceral cavity of a 3-month sham exposed rat. It can be seen that the visceral contents are heavily invested with fat, a condition which is normal for an animal which has been permitted food and water *ad libitum* for 3 months, accompanied with minimal physical exercise.

TABLE 2

CHANGES IN BODY AND TISSUE WET WEIGHTS RESULTING FROM 3 MONTHS INHALATION METHYL METHACRYLATE VAPOR[a]

Tissue	Sham control group (g)	Experimental group (g)
Whole body	226.70 ± 14.10 (16)	213.70 ± 13.90 (18)*
Brain	1.83 ± 0.05 (16)	1.83 ± 0.05 (16)
Lung	0.94 ± 0.10 (16)	0.84 ± 0.09 (16)*
Liver	5.89 ± 0.48 (16)	5.68 ± 0.47 (16)
Spleen	0.41 ± 0.03 (16)	0.39 ± 0.03 (16)*
R. kidney	0.71 ± 0.04 (16)	0.72 ± 0.06 (16)
L. kidney	0.71 ± 0.04 (16)	0.72 ± 0.05 (16)
R. adrenal	0.01 ± 0.01 (15)	0.02 ± 0.01 (16)
L. adrenal	0.02 ± 0.01 (16)	0.02 ± 0.01 (16)

[a] Rats were given methyl methacrylate (116 ppm) daily by the inhalatory route for 542 hours and killed 24 hours after the last exposure. Same in Tables 3 and 4. Abbreviations are: R., right; L., left. Same in Table 5. ( ) number of animals. Same in Tables 3 and 4.

* Statistically significant difference when compared with the mean values of sham control rats ($p < 0.05$).

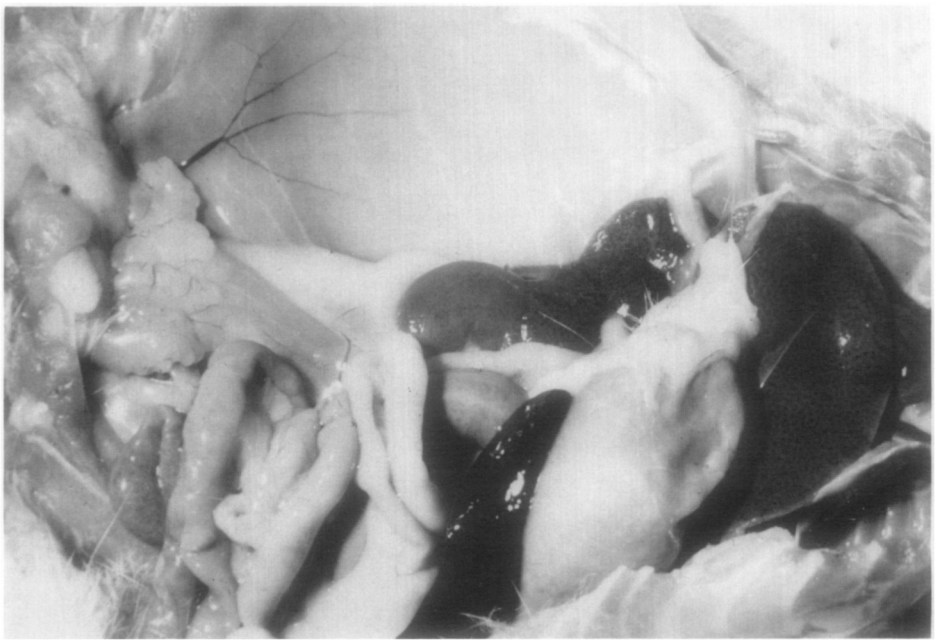

FIG. 4. Autopsy photograph of the appearance of the visceral cavity of a 3-month MMA exposed rat. It can be readily seen that the visceral cavity of this animal is markedly deficient in fat as compared to the control.

TABLE 3
HEMATOLOGIC EFFECTS OF 3 MONTHS EXPOSURE TO METHYL METHACRYLATE VAPOR[a]

Test	Sham control group	Experimental group
WBC ($\times 10^3$)	2.8 ± 0.8 (8)	2.9 ± 0.3 (6)
RBC ($\times 10^6$)	7.7 ± 0.4 (8)	7.4 ± 0.3 (6)
HGB (g)	15.2 ± 0.9 (8)	15.0 ± 0.2 (6)
HCT (%)	44.0 ± 2.0 (8)	44.0 ± 2.0 (6)
MCV ($m\mu^3$)	56.0 ± 3.0 (8)	58.0 ± 1.0 (6)
MCH ($m\mu g$)	19.3 ± 1.0 (8)	19.9 ± 0.9 (6)
MCHC (%)	34.9 ± 1.4 (8)	34.4 ± 1.5 (6)

[a] Abbreviations are: WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin, MCHC, mean corpuscular hemoglobin concentration. Mean experimental values are not significantly different from mean sham control values in all cases.

Results of the 6-Month Group

Upon necropsy, qualitative observations were not suggestive of any noticeable lack of visceral fat deposits of the exposed group when compared to the deposits of the sham control groups. Differences in the amount of subcutaneous fat were still apparent upon visual inspection, with the members of the exposed group showing less.

TABLE 4
SMA 12/60 BLOOD SERUM ANALYSES AFTER 3 MONTHS EXPOSURE TO METHYL METHACRYLATE VAPOR[a]

Test	Sham control group	Experimental group
T.P. (g%)	6.72 ± 0.40 (8)	6.84 ± 0.36 (8)
Alb. (g%)	4.02 ± 0.25 (8)	4.29 ± 0.47 (8)
Ca^{++} (mg%)	9.83 ± 0.52 (8)	9.76 ± 0.43 (8)
Inor. phos. (mg% P)	6.98 ± 0.22 (8)	7.26 ± 0.37 (8)
Ca^{++}/PO_4 = Ratio	1.40 ± 0.07 (8)	1.35 ± 0.07 (8)
Chol. (mg%)	71.00 ± 11.00 (8)	81.00 ± 13.00 (8)
Glu. (mg%)	166.00 ± 7.00 (8)	166.00 ± 10.00 (8)
BUN (mg%)	22.50 ± 5.80 (8)	28.60 ± 8.80 (8)
Uric acid (mg%)	1.97 ± 0.44 (8)	1.91 ± 0.19 (8)
Creat. (mg%)	0.64 ± 0.07 (8)	0.68 ± 0.11 (8)
T. Bili. (mg%)	0.40 ± 0.04 (8)	0.33 ± 0.13 (8)
Alk. Phos. (mU/ml)	278.00 ± 12.00 (8)	327.00 ± 29.00 (7)*
SGOT (mU/ml)	351.00 ± 70.00 (8)	420.00 ± 86.00 (7)

[a] Abbreviations are: T.P., total protein; Alb., albumin; Ca^{2+}, calcium; Inor. Phos., inorganic phosphate; chol., cholesterol; glu., glucose; BUN, blood urea nitrogen; Creat., creatinine; T. Bili., total bilirubin; Alk. Phos., alkaline phosphatase; SGOT, serum glutamate–oxaloacetate transaminase. Same in Table 6.

* Statistically significant difference when compared with the mean values of sham control rats ($p < 0.05$).

Weight data for the 6-month groups are summarized in Table 5. Mean body and popliteal fat pad weights were significantly lower in the case of the exposed group. Examination of SMA 12/60 data for the 6-month group, contained in Table 6, indicates that mean total serum protein, cholesterol, blood urea nitrogen, serum glutamate–oxaloacetate transaminase, and calcium/phosphate ratio were significantly lower in the case of the exposed group, while the mean serum alkaline phosphatase and inorganic phosphate concentrations were significantly elevated.

Table 7 indicates that the mean 15-minute percentage intestinal transit of an inert marker mixture was significantly lower in a group of exposed animals compared to controls. Both mean small intestinal length and mean intestinal length normalized for body weight were also significantly increased. The mean body weight of the exposed animals was lower than that of the sham exposed group with the lack of significance attributable to the small sample size.

DISCUSSION

Again, we have previously published data which indicate that exposure to high concentrations of methyl methacrylate monomer vapor produce an immediate, reversible reduction in gastric motor activities and tone in the conscious rat, similar gastrointestinal effects in the acute, anesthetized dog, and a reduction in gastric motor activity and tonus of a human volunteer who was merely exposed to an open container of the monomer in a closed room. *In vitro* exposure of strips of rat small intestine and guinea pig ileum (Mir *et al.*, 1973) results in an immediate reversible inhibition of spontaneous motor activity and a reduction in tonus.

In the above instances, the effects noted were immediate and reversible upon

TABLE 5
CHANGES IN BODY AND TISSUE WET WEIGHTS RESULTING FROM 6 MONTHS INHALATION METHYL METHACRYLATE VAPOR[a]

Tissue	Sham control group (g)	Experimental group (g)
Whole body	301.60 ± 21.90	287.70 ± 17.90*
Brain	1.95 ± 0.08	1.93 ± 0.09
Lung	1.05 ± 0.10	1.05 ± 0.16
Liver	6.72 ± 0.90	6.78 ± 0.89
Spleen	0.53 ± 0.04	0.52 ± 0.05
R. kidney	0.91 ± 0.08	0.92 ± 0.10
L. kidney	0.93 ± 0.07	0.92 ± 0.08
R. adrenal	0.03 ± 0.01	0.03 ± 0.01
L. adrenal	0.03 ± 0.02	0.03 ± 0.01
Epididymal fat pads	0.42 ± 0.06	0.39 ± 0.05
L. popliteal fat pad	0.22 ± 0.04	0.18 ± 0.03*

[a] Rats were given methyl methacrylate (116 ppm) daily by the inhalatory route for 1105 hours and killed 24 hours after the last exposure. Same in Tables 6 and 7. Means ± SD represents 26 animals in each group.

* Statistically significant difference when compared with the mean values of sham control rats ($p < 0.05$).

TABLE 6
SMA 12/60 BLOOD SERUM ANALYSES AFTER 6 MONTHS EXPOSURE TO METHYL METHACRYLATE VAPOR[a]

Test	Sham control group	Experimental group
T.P. (g%)	7.07 ± 0.33	6.74 ± 0.34*
Alb. (g%)	4.14 ± 0.22	4.08 ± 0.23
Ca^{2+} (mg%)	9.47 ± 0.43	9.19 ± 0.49
Inor. Phos. (mg% P)	5.47 ± 0.60	6.07 ± 0.53*
Ca^{2+}/PO_4 ≅ Ratio	1.75 ± 0.19	1.52 ± 0.12*
Chol. (mg%)	74.00 ± 8.00	67.00 ± 7.00*
Glu. (mg%)	106.00 ± 14.00	107.00 ± 12.00
BUN (mg%)	22.20 ± 2.30	18.90 ± 2.60*
Uric acid (mg%)	1.62 ± 0.34	1.61 ± 0.28
Creat. (mg%)	0.67 ± 0.08	0.62 ± 0.08
T. bili. (mg%)	0.54 ± 0.10	0.61 ± 0.15
Alk. phos. (mU/ml)	133.00 ± 52.00	181.00 ± 55.00*
SGOT (mU/ml)	425.00 ± 54.00	384.00 ± 47.00*

[a] Mean ± SD represents 14 animals in each group.

* Statistically significant difference when compared with the mean values of sham control rats ($p < 0.05$).

removal of the agent. We feel that it is reasonable to suspect that the immediate *in vivo* effects are due to the direct action of the agent upon the target tissues and that transport of the agent is mediated by the cardiovascular and pulmonary systems.

Chronic exposure is another matter, inasmuch as the agent has ample time to become well equilibrated with various compartments of distribution and to effect

TABLE 7
SMALL INTESTINAL TRANSIT PERFORMANCE AND RELATED DATA FOR 2-DAY FASTED RATS AFTER 6 MONTHS EXPOSURE TO METHYL METHACRYLATE VAPOR[a]

Parameter	Sham control group	Experimental group
Body weight (g)	303.00 ± 22.00	287.00 ± 13.00
Length of small intestine (cm)	103.00 ± 27.00	106.00 ± 16.00*
Normalized small intestinal length (cm/gm body weight)	0.34 ± 0.02	0.37 ± 0.02*
Length of small intestine transversed (cm)	71.00 ± 11.00	56.00 ± 21.00
Percentage of small intestine transversed (%)	69.00 ± 1.00	58.00 ± 4.00*

[a] Mean ± SD represents eight animals in each group.
* Statistically significant difference when compared with the mean values of sham control rats ($p < 0.05$).

both biological structure and biochemical function within those compartments. The extents to which chemical combination, alterations in detoxification mechanisms, and mechanism of excretion are affected as the result of chronic exposure to MMA vapor are unknown.

For that matter the rat may not be the best model of man. On a weight-for-weight basis the maximum permissible chronic exposure concentration for a rat could reasonably be scaled downward. Furthermore, the 6-month period of exposure would be equivalent to an 11-year exposure period for a human, assuming a lifespan of 3 years for the rat and 66 years for the human.

The fact remains that no spontaneous deaths occurred in those members of the population that were exposed for 6 months, or in the group which received the 3-month exposure regimen. In no case did the exposed animals behave in a way that would suggest to observers that they were "sick" to the point of appearing in distress, but their general appearance and grooming habits were different.

The lack of visceral fat in the 3-month exposed group was remarkable and was not as evident in the 6-month group, thus suggesting the not unreasonable possibility that this parameter, which is age-dependent and others which are also age-dependent, might be affected as functions of the absolute age of the rat.

The experimentally convenient epididymal fat pad in the rat has been used extensively for assessment of adipose tissue metabolism, but it may not be representative of the majority of the adipose tissue in the animal. Recently Kannan and Baker (1975) reported that in the fasted mouse, refed with radioactive glucose, adipose tissue from the popliteal region of the leg muscle had a specific activity 10 times greater than epididymal adipose tissue. This fat pad was also found to contain more than half the ^{14}C-fatty acids in the entire leg muscle, and substantial weight changes were observed in response to fasting. The significant weight reduction in the popliteal fat pad as compared to the nonresponsive epididymal fat pad, may be a result of greater metabolic activity, as demonstrated in the homologous popliteal fat pad of the mouse. The overt lack of fat at 3 months, suggests that total body weight reduction in these animals probably is related to the degree of adiposity. The fact

that the animals did not show gross changes in visceral adiposity after 6 months of MMA vapor exposure as compared to 3 months may be a result of (1) altered nutritional status of the colony during the latter phase as compared to the first 3 months, or (2) metabolic changes in adipose tissue with age (Altschuler *et al.*, 1962).

Although cholesterol, blood urea nitrogen, inorganic phosphate, and serum glutamate–oxaloacetate transaminase have been determined to be statistically significant at 6 months postexposure, the differences are too small for interpretation. For example, we are bound in advance to our established criteria of significance, but it should be noted that the nonsignificant changes in serum cholesterol in the 3-month group were opposite in direction to the significant changes in the 6-month group, with the lack of significance of the former probably related to the small sample size. Significant and nonsignificant mean values of the calcium/phosphate ratios are similarly within normal limits. The decrease in total plasma protein should be in the globulin fraction since the albumin concentration did not change. The 35% increase in alkaline phosphatase at 6 months is not only significant, but consistent with the change at 3 months. In the fasted rat, most of the serum alkaline phosphatase is of bone origin (Righetti and Kaplan, 1971). The higher alkaline phosphatase values at 3 months in all animals merely reflect the greater osteoblastic activity of younger rats. The origin of the alkaline phosphatase increases cannot be determined from the data, but liver, bone, and intestinal tissues are the most reasonable possibilities (Kaplan and Kaplan, 1970; Righetti and Kaplan, 1971).

We tentatively regard the significant and possibly significant differences in these various parameters as indicating that the operations of the related homeostatic systems were changed in a manner suggestive of an alteration in set-point. At present we have not completed our studies of structure and ultrastructure which would be necessary to associate the alteration in any parameter value with observable structural alteration or damage. The observations which we report as being associated with the chronic-inhalatory exposure to the maximum allowable dosage of MMA vapor have not previously been reported by other workers. Because of the care which was exercised in the design and conduct of the exposures and sampling procedures we have confidence in these results. In all cases none of the observations was made immediately upon cessation of the last exposure, but at least 16 hours later (the next morning).

In the case of the intestinal transit animals, 3 days had elapsed due to the fasting requirement. Thus all changes must be viewed as belonging to a different category than those immediate changes in gastrointestinal motor activities which returned to control values within minutes after removal of the gas. Again, in the cases of the transit animals, we feel that the significantly larger mean value of small intestinal length for the exposed animals was probably due to a loss in smooth muscle tonus and is explained, in part, by the decreased transit rate which was observed. Whether observed changes can be inferred to return to control values in a time-dependent manner remains to be seen. Similarly, future investigations will be required to determine the mechanisms responsible for the observed effects as well as the distribution of the gas within various tissues and fluid compartments.

ACKNOWLEDGMENT

The excellent technical assistance of Mr. Harold Perrong is gratefully acknowledged.

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