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UPDATE ON THE TOXICITY OF INHALED METHYL METHACRYLATE VAPOR

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ABSTRACT

The current threshold limit value (TLV) of 100 ppm for methyl methacrylate vapor was originally set because it was considered to be a value sufficiently low to preclude either systemic toxicological effects or discomfort from irritation in workers chronically exposed to the vapor. Shortly after this limit was proposed we became interested in evaluating the toxicological properties of methyl methacrylate vapor and, subsequently, of providing experimental data which would be useful in evaluating the adequacy of this TLV. The purpose of this article is to review some of the more relevant literature prior to 1976 which pertains to inhalation exposure and to summarize our more recent data which resulted from statistically designed studies employing acute and subchronic exposures to known concentrations of the vapor including the near-TLV value of 116 ppm.

INTRODUCTION

Interest in the toxicity of methyl methacrylate monomer continues because of its continued widespread use in commercial fabrications, its routine use in the practice of dentistry, and because of its employment as a bone cement. Other chronic medical uses include artificial knees, artificial shoulder joints, cranial

defect repairs, plastic splints and fusion in spine stabilization. However, the clinical literature pertaining to the employment of methyl methacrylate has, in recent years, become so voluminous that a detailed survey of applications cannot be given here. Then, again, in most cases the clinical literature does not contain precise toxicological information.

Autopolymerization formulations containing methyl methacrylate are employed in dentistry for prosthesis fabrication or stabilization. Here the mixing of components is usually done in an open container and the escape of the monomer vapor is evidenced by the penetrating odor which pervades the laboratory. At Temple, approximately 150 dental students may be fabricating custom acrylic trays, base plates or denture bases in one large laboratory. The individual exposure duration may be from three to six hours per day. The acrid odor that permeates the building during such large-scale use of methyl methacrylate in the technique laboratories is evidence of a high ambient concentration of the monomer vapor. Since, in the course of dental application, the initial heavy paste-like resin mix is frequently shaped using the bare hands, it should follow that absorption of methyl methacrylate may occur through the lungs and skin.

Direct contact with the liquid monomeric form is limited and accidental, but the primary vapor hazard occurs when the monomer is manufactured, stored, and used, either in medicinal or industrial application. Extensive reviews[1,2] on the subject of methyl methacrylate toxicity have been published. And, as a result, the toxicity of the material is well known and no one would attempt to

routinely expose his skin or eyes to direct contact, much less ingest it either voluntarily or, because of its pungent odor, by accident. Despite these facts, most of the experimental toxicological work done involves direct exposure, either by gastric or parenteral administration of the liquid monomer. While there is some justification for developing system and organ toxicity data from such exposures, there was a historical lack of data pertaining to inhalatory exposures and resulting toxicity.

ACUTE TOXICITY

LC_{50}

One of the earliest reports of inhalatory exposure toxicity which is always cited is the paper of Deichmann[3] which appeared in 1941. Deichmann showed that rabbits, guinea pigs and rats survived inhalation of methyl methacrylate in air at a concentration of 14.3 mg/l for eight hours. He also showed that a methyl methacrylate concentration of 19 mg/l killed all rabbits, guinea pigs and rats in two and one half to five hours. A later attempt by Spealman, Main, Haag, and Larson[4] employed mice, guinea pigs and dogs which were exposed for periods ranging from 30 minutes per day to three hours per day for periods ranging from three days to 15 days to calculated vapor concentrations between 39.3 mg/l and 65.5 mg/l. From their observations they estimated a three hour inhalation LD_{50} of methyl methacrylate in air for mice at 55.0 mg/l. In 1964, Borzelleca and his co-workers[5] reported that the LD_{50} for two hour exposures in rats was estimated to lie between 45 and 50 mg/l.

There is no doubt that part of the reason for the paucity of hard data pertaining to inhalatory exposure was directly attributable to a lack of good equipment for obtaining uniform exposure concentrations and to the inadequacy of available methods for verifying the magnitude and consistency of such exposure concentrations. In fact there were no consistencies apparent in methyl methacrylate LC_{50} data for short exposure periods until recently when we reported a four hour LC_{50} concentration of 7093 ppm for rats.[6] This is within a factor of two of the value of 4750 ppm which Deichmann[3] reported in 1941 for two rats. A survey of the relevant papers indicates that in those cases where dosimetry was in fact attempted with some care[3], or non-existant,[4,5] the experimental populations were extremely small and the experiments themselves were neither designed for nor analyzed by statistical methods. Obviously the other reason for scanty inhalatory toxicology data was the fact that the imperative for both setting and evaluating TLV standards is a relatively recent occurrence.

SUBCHRONIC TOXICITY

We set out to rectify some of the aforementioned shortcomings in inhalatory studies when we became interested in the toxicity of methyl methacrylate vapor in 1973.[7] Interestingly enough, we began our studies like everyone else: with calculated concentrations, enormous dosages, small sample sizes, and uncertain delivery systems. Our original observation[7] that inhalatory exposure to methyl methacrylate vapor caused a reduction in gastrointesti-

nal motor activities was subsequently confirmed both *in vitro*[8] and *in vivo*.[9,10]

Our interest in accurately determining exposure concentrations and in the statistical design of experiments stemmed from the need arising from the burgeoning interest in evaluating TLV concentrations of methyl methacrylate and other substances. Consequently most of the information of this nature has come from our laboratories since 1976. In fact we are aware of only one other paper[11] pertaining to methyl methacrylate inhalatory toxicity (an accidental death of a rhesus monkey) which had appeared in the literature since that time.

Body Weight and Gross Metabolic Performance

Data cited in previous reports[10] from our laboratories have indicated that rats which had received a daily eight hour exposure to approximately 116 ppm of methyl methacrylate vapor in air for three months, excluding weekends, had, on the average, lower body weights than those of a similar group which had received sham exposures. There was a readily apparent lack of fat deposits within the abdominal cavities of the exposed animals when they were examined at necropsy. Furthermore, when skinned, the carcasses of the exposed rats were obviously lean. Similarly, the mean body weight and the mean weight of the left popliteal fat pads of six month exposed rats were significantly less than those for the sham group.

We subsequently determined that these changes are only

observed in rats whose food intakes were severely restricted.[12] They are not observed in control rats whose food intake is restricted nor in methyl methacrylate exposed rats whose food intake is not restricted.[12] The preceding experiments demonstrate that under normal feeding conditions there are no methyl methacrylate induced effects upon such classical metabolic parameters as food and water intake or fluid output in rats.

We have no experimental data that account for the decreased body weight and subcutaneous fat phenomena[10] other than to point out that individual oxygen consumption measurements made for methyl methacrylate exposed and sham exposed rats picked at random at the end of the exposure period revealed increases of up to 45 percent in oxygen consumption on the part of the methyl methacrylate exposed animals.[13]

Blood Chemistries

We have employed near TLV (116 ppm) doses for three and six months[10,12] and 1000 ppm exposures for seven days.[13] SMA 12/60 blood serum component concentration changes have been noted at all gas concentrations employed, but the changes are not consistent and when significant, frequently in the wrong direction to have physiological significance.

Mean SMA 12/60 data indicate that we were able to conclude that the only significant difference which existed between the mean parameter values for the three month exposed and sham exposed groups (food restricted) was the mean serum alkaline phosphatase concentration of the exposed group which was significantly ele-

vated.[10] Non food-restricted rats which were chronically exposed for three months to daily concentrations of 116 ppm of methyl methacrylate vapor in air did not exhibit an elevated serum alkaline phosphatase.[12] SMA 12/60 blood serum analysis from these non food-restricted animals at necropsy resulted in a significant decrease in total bilirubin and an increase in total cholesterol.[12]

Examination of SMA 12/60 data for the six month food restricted group 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 methyl methacrylate exposed group, while the mean serum alkaline phosphatase and inorganic phosphate concentrations were significantly elevated.[10]

Six of the 14 observed parameter means were observed to be significantly lower in the 1000 ppm methyl methacrylate exposed (non food-restricted) group than those of the sham control group. These included albumin, glucose, blood urea nitrogen, serum glutamate-oxaloacetate transaminase, serum glutamate-pyruvate transaminase, and the albumin-glucose ratio.[13] Comparison of these results presents difficulties inasmuch as some of the rats were food restricted and others were not. Furthermore, while statistically significant differences in mean parameter values could be shown to exist between sham and exposed groups having the same dietary regimen, the differences themselves were frequently in the wrong direction to have known diagnostic value or the mean values for the exposed groups still fell within the normal range of values for the particular breed of rat (Sprague Dawley).

Cardiovascular Functions

No significant changes in heart rate or systemic arterial blood pressure were observed in beagle dogs that were exposed daily to 100 and 400 ppm of methyl methacrylate vapor for three months.[14] The transient hypotension which we initially reported in the anesthetized dog[9] and which has been observed by others[15] appears to be an acute effect.

Multiunit Activity in the Central Nervous System

Recent studies from our laboratory reported depression of multiunit electrical activity in the lateral hypothalamus and ventral hippocampus of rats which were exposed to 400 ppm of methyl methacrylate vapor in air for 60 minutes.[16] In sharp contrast, recordings made from the parietal cortex, cerebellum, dorsal hippocampus, medial amygdala, ventral medial hypothalamus, anterior hypothalamus, septum, and mammillary body following comparable exposures showed insignificant changes in multiunit electrical activity.[16]

Histopathology

Preliminary histological observations of sections from the livers of rats chronically exposed to daily concentrations of 116 ppm methyl methacrylate vapor in air for three and six months indicated the possible presence of frank liver damage in both groups.[17] Inasmuch as such changes were neither quantifiable nor consistently observed, a test of liver function was made in mice to determine whether it could be inferred that mean sleeping times

of mice intermittently exposed for 160 hours to 100 ppm and 400 ppm of methyl methacrylate vapor in air were significantly different than the mean sleeping time of a sham exposed group. Our results of decreased sleeping time in mice exposed to 100 ppm and 400 ppm of methyl methacrylate vapor do not support an assumption of impaired liver function.[13] However, Lawrence and Autian[18] have reported significant increases in sleeping time at much higher methyl methacrylate vapor concentrations (164.22 mg/l).

The lack of any remarkable gross or microscopic pathology at all dose levels in the case of the heart, gastrointestinal tract, spleen and adrenals is in good agreement with the negative findings of four other investigators who employed large doses by other routes of administration.[3-5,19]

Preliminary unpublished observations from our original studies also suggested that chronic exposure of rats to 116 ppm of methyl methacrylate in air might be associated with damage to tracheal epithelium. Scanning electron micrographs of the tracheal epithelia from rats and frogs have shown denudation of microvilli and suggestions that the ciliary morphology were altered at exposure concentrations of 400 ppm. We did not observe this for near TLV concentrations. The significance of chronic exposure to methyl methacrylate upon the function of respiratory ciliated epithelium was studied using adult northern grass frogs exposed to 116 ppm and 400 ppm of methyl methacrylate in air by means of measurements of the rate of transport of small glass spheres.[13] 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 five trials) in those frogs which had been exposed to the higher dosage. Thus, in keeping with its previously reported depressant effect upon active contraction,[7-10] methyl methacrylate in concentrations of about four times the TLV might exert a definite ciliostatic effect.

Teratology

We did not observe significant differences in proportions of fetal resorptions or teratogenic manifestations in the fetuses of pregnant mice that were exposed for 60 hours to 116 and 400 ppm of methyl methacrylate vapor in air.[20]

Gastrointestinal Motility

Except for the effect on body weight and body fat noted in rats chronically exposed to methyl methacrylate vapor with restricted diets, none of the above effects have been consistently observed at near TLV concentrations for the indicated durations of exposures. The most consistent responses, *in vivo* and *in vitro*, regardless of delivery route or dose, have continued to be elicited by the small bowel. Colonic activity, as evidenced by increased fecal excretion also appears to be influenced in rats.[12]

Small intestinal transit performance is depressed in rats exposed to near TLV values for three months or longer even though the measurements are made three days after termination of exposure on a near-starvation background.[10] Acute *in vivo* and *in vitro*

experiments by ourselves, and by others[21] indicate that methyl methacrylate itself produces a transient motor depression of this organ. The effect disappears when the agent is removed. The acute methyl methacrylate effect does not possess atropine-like properties because the bowel produces an acetylcholine response in the presence of the agent.[22] The depressant effect on the small bowel persists even after pretreatment by the alpha adrenolytic phenoxybenzamine, thus suggesting that the effect does not involve adrenergic receptors.[22]

Experiments with dogs[9] support the *in vitro* data and lead to the conclusion that the acute effect is not a result of long arc reflexes. Evidence that the acute affect is not due to short arc reflexes involving the plexus of Auerbach consists of the observation that the motor inhibitory effect is evident in rat uterine smooth muscle which does not have this plexus.[22] Preliminary results from this laboratory suggest that acute methyl methacrylate exposures of frogs are associated with decreases in twitch force produced by frog skeletal muscles.[23] Other preliminary observations have indicated that similar depressant effects upon gastrointestinal smooth muscle are also produced *in vivo* and *in vitro* by ethyl acrylate and butyl acrylate, with these agents appearing to produce the same effects at lower concentrations and dosages.[24]

These data suggest that the motor inhibitory effect may encompass more than one acrylic acid ester, and that the smooth muscle of the small intestine constitutes a particularly sensitive

model for both the evaluation of the toxic effect and an elucidation of the inhibitory mechanism.

We have not discarded a very early suggestion that methyl methacrylate in particular may exert its effect by reducing the contractile force produced by either skeletal or smooth muscle. The questions are not answered whether the effect is upon the muscle membrane, and/or the contractile mechanism, and whether visceral and multiunit smooth muscle, skeletal muscle, and cardiac muscle also constitute sensitive effector systems. An investigation of the mechanisms of the inhibitory effect and a comparison of responses with different types of muscle would be necessary to validate any kind of muscle as a sensitive model or choice for evaluating acrylate toxicity.

DISCUSSION AND CONCLUSIONS

No update on the toxicology of any substance is complete today without reference to its carcinogenicity. "The carcinogenic potential of methyl methacrylate in humans is unknown".[2] No epidemiological data have been analyzed to determine whether the incidence of various malignancies is higher in occupationally exposed groups than in non-exposed groups and/or whether smoking is a related factor. In any event, dosimetry in these cases present a formidable problem.

In a like manner, no current data exists which justify the definition of routine occupational exposure to methyl methacrylate vapor as being hazardous. Recent studies from this laboratory indicate that gastrointestinal motor activities may constitute a

sensitive physiological system which is affected by inhalation of relatively low concentration of this vapor. The existence of such effects has been hitherto unsuspected. Thus, there has been no reason to seek an association between occupational exposure to these vapors and gastrointestinal disease or distress. The consensus of this work is that visceral smooth muscle and possibly other contractile systems may constitute models which can be used to evaluate acute toxic mechanisms.

However, at this point it may be well to indicate that, aside from the effects previously noted, methyl methacrylate is known to be a powerful irritant. It can produce cellular responses. If an alteration of liver function in favor of decreased sleeping time is subsequently confirmed, such confirmation will provide some reason to suspect that either methyl methacrylate, a metabolite, or a substance related to them produces an effect at the level of the genome of liver cells in the mouse. A few other points of interest may be noted without discussion in this place. The observations of focal lesions of the tracheas of rats and frogs suggest that an irritative process has occurred. We do not know whether the absence of cilia and particularly microvilli is necessarily a manifestation of cellular damage or whether it is an equally likely manifestation of cellular immaturity resulting from a proliferative response. Thus, if the objective is to examine the adequacy of a TLV which has been set with due regard to known pathological data and common sense, then the places to begin are those areas where cellular responses seem likely.[13]

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