PB88-247648

Methyl Methacrylate Induced Changes in CNS (Central Nervous System) Activity

Temple Univ., Philadelphia, PA

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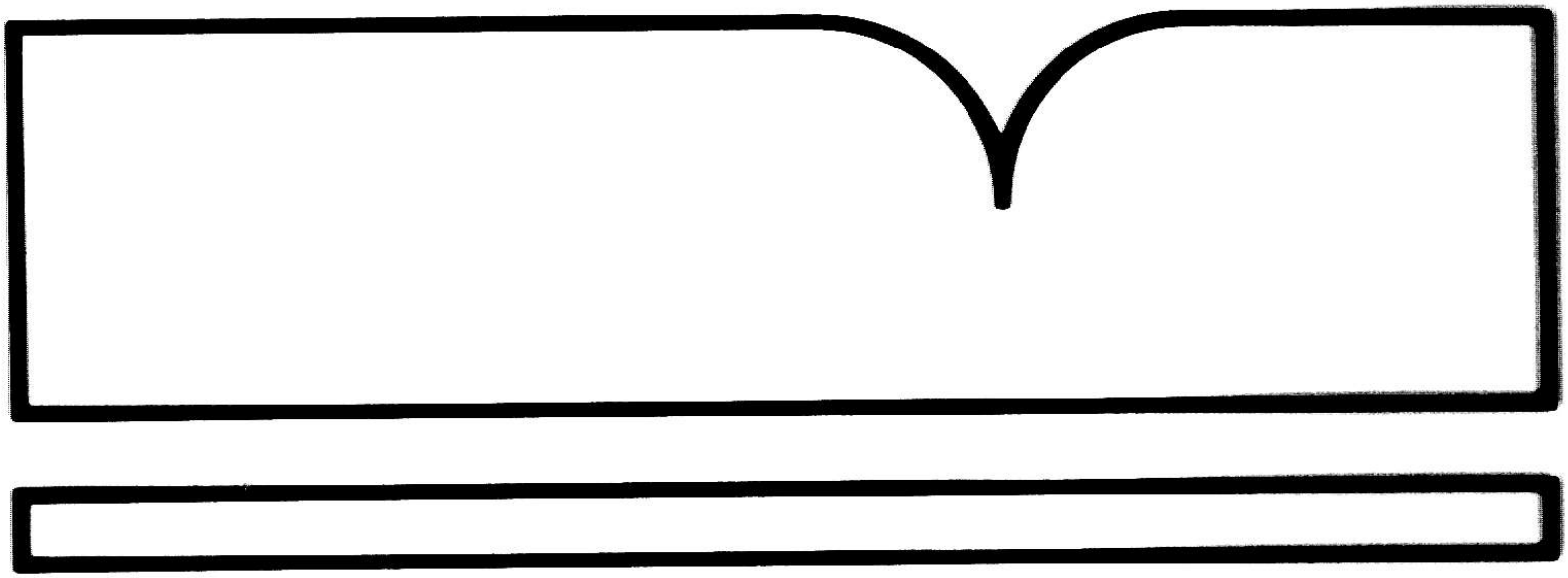
1980



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PB88-247648

TERMINAL PROGRESS REPORT

TITLE OF PROJECT

Methyl Methacrylate Induced Changes in CNS Activity

GRANT NUMBER

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PRINCIPAL INVESTIGATOR

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16. Abstract (Limit: 200 words)

Experiments were performed to determine if methyl-methacrylate (80626) (MMA) monomer vapor in air caused central nervous system (CNS) changes in exposed rats. Rats were exposed to 400 parts per million (ppm) MMA vapor for 60 minutes. The only significant changes to develop occurred in the lateral hypothalamic and ventral hippocampal nuclei. Several substudies conducted to better understand these results suggested that the changes in the hippocampal neuronal firing rates were related to the perception of the MMA odor and dependent on the presence of an intact nervous connection to the receptors in the nose. In a subchronic study animals were exposed for 2 to 10 weeks to 400ppm MMA vapor. No consistent long term changes in neuronal activity were detected. However, a decrease in neuronal activity was detected during the first week of exposure. In another study the exposure levels of MMA ranged from 50 to 800ppm. The lateral hypothalamic and ventral hippocampal nuclei responded as before, but not at the 50ppm level. From this data the author concludes that the threshold exposure concentration for the observed effects are the same as or slightly less than the current threshold limit value for MMA vapor in the workplace.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms

NIOSH-Publication, NIOSH-Grant, Grant-Number-OH-00740-02, Plastics-industry, Nervous-system-disorders, Inhalation-studies, Vapors, Laboratory-animals, Central-nervous-system, Toxic-effects

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
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SUMMARY STATEMENT

The proposed experiments were designed:

1. To determine whether methyl methacrylate (MMA) monomer vapor in air produces an effect on the central nervous system in acutely exposed rats.

2. To determine whether significant central nervous system effects are produced in rats during chronic exposures to the monomeric methyl methacrylate vapor at a concentration four times that of the currently accepted industrial limit for occupational exposure.

RESULTS

A. ACUTE PHASE

As evidenced by the data from the following communications:

1. Innes, D.L., M.F. Tansy and J.S. Martin. Effects of acute methyl methacrylate inhalation on rat brain neuronal activity. Journal of Dental Research, 58: 208, 1979.

2. Innes, D.L. and M.F. Tansy. Methyl methacrylate vapor and multi-unit activity in the rat brain. Journal of Dental Research, 59: 393, 1980.

it was demonstrated that only the lateral hypothalamic and ventral hippocampal nuclei showed any significant alterations in multi-unit neuronal activity during the 60 min inhalation exposure to 400 ppm of MMA vapor in room air. All other (Table I) nuclei examined failed to demonstrate a significant change from control states. The alteration in neuronal activity was a marked slowing of the neuronal firing rate, which returned towards the pre-exposure level when the animal was returned to room air. The cerebellar nuclei also demonstrated a reduction in firing rates during exposure to 400 ppm of MMA vapor, but this lowering of activity was not different from the slowing observed during room air exposed control animals. It was concluded that the cerebellum was reflecting the decreased motor activity associated with the anesthetic and not the MMA vapor.

As suggested in the original protocol, several sub-studies were performed to determine the nature of this response to the MMA vapor. The first sub-study was undertaken to rule out the observed effects as being due only to perception

of an odor. Each rat, before exposure to 400 ppm of MMA vapor, had a bilateral electrolytic lesion placed within the olfactory nerves, which was later verified by histologic technique. Only the lateral hypothalamic and ventral hippocampal nuclei were examined as responding structures and the amygdaloid nucleus was used as the control-nonresponding structure. As seen in the data (Table II) the lateral hypothalamic nucleus did not alter its response to the MMA vapor. However, the ventral hippocampal nucleus no longer displayed the decreased neuronal firing rate in response to the MMA vapor. The results of sham lesion studies were the same as the MMA exposure studies, indicating that the responses observed in the ventral hippocampal nucleus were dependent on an intact nerve supply. It is concluded, based on the concept that one of the major functions of the limbic brain is odor recognition, that the observed changes in hippocampal neuronal firing rates were related to the perception of the MMA odor and was dependent upon the presence of an intact nervous connection to the receptors in the nose. The continued response on the part of the lateral hypothalamic nucleus suggests that this effect is mediated via the blood, which has picked-up the MMA monomer during its passage through the lungs.

The second sub-study was to determine the specificity of the response. Animals were exposed, using identical conditions, to either butylacrylate (a chemically related compound to MMA) or eugenol (a non-chemically related compound but highly odoriferous). The ventral hippocampal nucleus responded only to the eugenol demonstrating some specificity in odor recognition (Table III). In contrast, the lateral hypothalamic nucleus clearly responded to both chemicals. The response recorded by the lateral hypothalamus is obviously not specific to just the MMA monomer and may be acting as a general chemoreceptor capable of responding to various foreign chemicals present in the blood. This suggests the unique possibility of using this nucleus as a target tissue for future inhalatory studies. The remaining nuclei did not show any response to these chemicals with the exception of the parietal cortex. Inexplicable at present is the fact that eugenol induced an alteration in the parietal cortex.

B. CHRONIC PHASE

Following the identification of the two responding nuclei to the acute effects of MMA, a subchronic study was undertaken. A total of 51 animals with permanent electrodes in the lateral hypothalamic, ventral hippocampal and amygdaloid

(control) nuclei were studied. Exposure duration, for those animals reported, ranged from 2 weeks (70 hours) to 10 weeks (350 hours). In spite of numerous precautions, the death rate due to infection and/or starvation (electrodes placed in areas of the brain associated with satiation and feeding behaviors), was high such that an additional 70 animals were lost before meaningful data could be obtained. The results of chronic exposure to 400 ppm of MMA vapor indicated that no consistant long-term changes in neuronal activity could be detected under the conditions employed. There was, however, a decrease in neuronal activity detected during the first week of exposure to the MMA vapor. This effect was very reminescent of the acute study data as only the lateral hypothalamus and ventral hippocampus were involved. This response was variable and therefore not significant. By the second week of the study the response had dissappeared suggesting an adaptation to the effects of the MMA vapor. It was deemed unnecessary to pursue this study with the two lesser concentrations of MMA because of the lack of a long-term response at the highest dose-level and the large numbers of animals consumed and not budgeted.

OTHER STUDIES

As can be seen in Table IV the majority of the original nuclei were examined in this sub-study. Animals were acutely exposed to the MMA monomer, but with the concentrations ranging from 800 to 50 ppm. Both the lateral hypothalamic and ventral hippocampal nuclei responded, as before, to the MMA vapor until the 50 ppm concentration was reached. At this concentration the response was no longer significant. However, one-half of the animals tested still showed a definite response to the MMA vapor at this low concentration. In addition, it should be noted that the anterior hypothalamic nucleus demonstrated a significant increase in neuronal activity at the 50, 100 and 800 ppm exposure levels. The response was elevated but not significant at the 200 and 400 ppm explaining why it had not been noted earlier. Due to instrumentation limitations no meaningful interpretation can be ascribed to this response.

In summary, it is concluded that acute and chronic respiratory tract exposures to MMA vapor in air are associated with significant alterations in neuronal activity in at least two areas of the rat brain. We have identified the lateral hypothalamus and ventral hippocampus as nuclear regions wherein the cellular response to the MMA stimulus was associated with a decreased rate of firing. We observed significantly reduced activities in the lateral hypothalamus and ventral hippocampus at exposures of 100 ppm but not at 50 ppm. It would appear that the threshold exposure concentration for these effects are the same as or slightly less than the current threshold limit value (TLV) for methyl methacrylate monomer vapor.

TABLE I

EFFECTS OF MMA MONOMER INHALATION AT 400 PPM VERSUS ROOM AIR ON THE MULTIPLE-UNIT ACTIVITY RECORDED FROM VARIOUS RAT BRAIN NUCLEI

	ROOM AIR $\bar{X} \pm$ SD	(N)	400 PPM MMA $\bar{X} \pm$ SD	(N)
HYPOTHALAMIC NUCLEI				
Anterior	- 0.2 ± 17.8	(14)	17.2 ± 26.9	(10)
Dorsal	15.2 ± 67.9	(13)	- 6.6 ± 13.9	(10)
Lateral	10.7 ± 29.1	(16)	-15.2 ± 13.9*	(19)
Ventromedial	24.1 ± 52.7	(9)	48.4 ± 68.0	(9)
Mammillary body	16.6 ± 34.9	(12)	32.4 ± 63.1	(9)
LIMBIC NUCLEI				
Amygdaloid	17.7 ± 33.0	(14)	87.8 ± 186.8	(11)
Dorsal hippocampal	126.8 ± 285.2	(6)	13.5 ± 5.9	(5)
Ventral hippocampal	0.5 ± 23.1	(10)	-21.3 ± 29.7*	(16)
Septal	10.1 ± 17.6	(10)	4.1 ± 17.4	(12)
CEREBRAL NUCLEI				
Parietal cortex	27.4 ± 45.0	(16)	45.3 ± 59.0	(16)
Cerebellar cortex	-39.2 ± 28.9	(7)	-31.7 ± 35.1	(8)

* - Significant at $P < 0.05$ for both the Student's t test and the Mann-Whitney test
$\bar{X}$ - Average percent change in neuronal activity from pre-exposure control levels
SD - Standard Deviation
N - Number of animals investigated

TABLE II

EFFECTS OF SHAM LESIONS AND DESTRUCTION OF THE OLFACTORY PATHWAYS ON MULTIPLE-UNIT ACTIVITY RECORDED FROM VARIOUS RAT BRAIN NUCLEI DURING INHALATION EXPOSURE TO 400 PPM MMA VERSUS ROOM AIR

	ROOM AIR		SHAM LESION 400 PPM MMA		NOSE LESIONED 400 PPM MMA	
	$\bar{X} \pm$ SD	(N)	$\bar{X} \pm$ SD	(N)	$\bar{X} \pm$ SD	(N)
HYPOTHALAMIC NUCLEI						
Anterior	- 0.2 ± 17.8	(14)	1.7 ± 15.2	(8)	8.2 ± 16.6	(7)
Dorsal	15.2 ± 67.9	(13)	- 4.8 ± 21.6	(8)	30.2 ± 46.9	(10)
Lateral	10.7 ± 29.1	(16)	- 3.7 ± 4.9*	(4)	-21.2 ± 22.4*	(17)
Mammillary body	16.6 ± 34.9	(12)	-28.6 ± 53.0	(2)	-10.9 ± 60.0	(2)
LIMBIC NUCLEI						
Amygdaloid	17.7 ± 33.0	(14)	27.7 ± 20.1	(3)	19.2 ± 40.9	(7)
Ventral hippocampal	0.5 ± 23.1	(10)	-32.8 ± 34.9*	(8)	98.0 ± 282.6	(12)
Septal	10.1 ± 17.6	(10)	13.4 ± 14.6	(10)	18.6 ± 19.4	(14)
CEREBRAL NUCLEI						
Parietal cortex	27.4 ± 45.0	(16)	36.2 ± 27.6	(3)	- 1.0 ± 46.7	(11)

* - Significant at $P < 0.05$ for both the Student't t test and the Mann-Whitney test
$\bar{X}$ - Average percent change in neuronal activity from pre-exposure control levels
SD - Standard Deviation
N - Number of animals investigated

TABLE III

EFFECTS OF BUTYLACRYLATE AND EUGENOL VERSUS ROOM AIR ON THE MULTIPLE-UNIT ACTIVITY RECORDED FROM VARIOUS RAT BRAIN NUCLEI

	ROOM AIR		BUTYLACRYLATE 100 PPM		EUGENOL	
	$\bar{X} \pm SD$	(N)	$\bar{X} \pm SD$	(N)	$\bar{X} \pm SD$	(N)
HYPOTHALAMIC NUCLEI						
Dorsal	15.2 ± 67.9	(13)	- 1.6 ± 23.0	(3)	- 1.7 ± 14.4	(3)
Lateral	10.7 ± 29.1	(16)	- 5.1 ± 12.2*	(14)	- 7.6 ± 20.8*	(16)
Mammillary body	16.6 ± 34.9	(12)	11.9 ± 21.3	(7)		
LIMBIC NUCLEI						
Amygdaloid	17.7 ± 33.0	(14)	21.8 ± 48.0	(9)	18.6 ± 15.3	(11)
Ventral hippocampal	0.5 ± 23.1	(10)	- 9.2 ± 28.6	(7)	-26.9 ± 32.6*	(8)
Septal	10.1 ± 17.6	(10)	4.7 ± 5.3	(6)	16.4 ± 14.0	(9)
CEREBRAL NUCLEI						
Parietal cortex	27.4 ± 45.0	(16)	- 2.1 ± 21.7	(8)	-15.1 ± 21.1*	(10)

* - Significant at $P < 0.05$ for both the Student's t test and the Mann-Whitney test
$\bar{X}$ - Average percent change in neuronal activity from pre-exposure control levels
SD - Standard Deviation
N - Number of animals investigated.

TABLE IV

EFFECTS OF VARYING THE CONCENTRATION OF MMA MONOMER VAPOR VERSUS ROOM AIR ON THE MULTIPLE-UNIT ACTIVITY RECORDED FROM VARIOUS RAT BRAIN NUCLEI

	ROOM AIR $\bar{X} \pm$ SD	(N)	50 PPM MMA $\bar{X} \pm$ SD	(N)	100 PPM MMA $\bar{X} \pm$ SD	(N)	200 PPM MMA $\bar{X} \pm$ SD	(N)	400 PPM MMA $\bar{X} \pm$ SD	(N)	800 PPM MMA $\bar{X} \pm$ SD	(N)
HYPOTHALAMIC NUCLEI												
Anterior	- 0.2 ± 17.8	(14)	31.0 ± 24.2*	(10)	64.1 ± 108.9*	(8)	8.4 ± 36.2	(5)	17.2 ± 26.9	(10)	38.9 ± 20.9	(12)
Lateral	10.7 ± 29.1	(16)	10.7 ± 19.9	(14)	-18.1 ± 31.1*	(13)	-14.0 ± 10.8*	(8)	-15.2 ± 13.9*	(19)	-21.4 ± 22.4*	(14)
Ventromedial	24.1 ± 52.7	(9)	12.1 ± 10.0	(6)	117.1 ± 12.6*	(8)	15.7 ± 41.5	(4)	48.4 ± 68.0	(9)	22.2 ± 43.7	(4)
Mammillary body	16.6 ± 34.9	(12)	- 0.3 ± 20.4	(9)	6.2 ± 15.9	(6)	-11.0 ± 14.1	(2)	32.4 ± 63.1	(9)	51.5 ± 78.1	(4)
LIMBIC NUCLEI												
Amygdaloid	17.7 ± 33.0	(14)	28.9 ± 29.8	(15)	30.7 ± 35.8	(12)	17.7 ± 33.0	(14)	87.8 ± 186.8	(11)	22.5 ± 66.8	(16)
Ventral hippocampal	0.5 ± 23.1	(10)	15.7 ± 6.0	(7)	-17.4 ± 17.8*	(8)	-10.1 ± 16.6*	(7)	-21.3 ± 29.7*	(16)	-11.9 ± 12.4*	(10)
Septal	10.1 ± 17.6	(10)	15.4 ± 24.0	(9)	66.5 ± 80.7	(10)	24.5 ± 39.4	(8)	4.1 ± 17.4	(12)	45.3 ±114.4	(15)
CEREBRAL NUCLEI												
Parietal cortex	27.4 ± 45.0	(16)	21.9 ± 15.6	(15)	41.6 ± 36.3	(10)	40.7 ± 24.8	(8)	45.3 ± 59.0	(16)	47.7 ± 93.6	(16)

* - Significant at $P < 0.05$ for both the Student's t test and the Mann-Whitney test
$\bar{X}$ - Average percent change in neuronal activity from pre-exposure control levels
SD - Standard Deviation
N - Number of animals investigated.

9

FORM A

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ABSTRACTS MUST BE RECEIVED BY OCTOBER 15, 1978

Complete: Items 1—5 below and type abstract within box, following instructions on reverse side.
Submit: Form A—Original and 4 Xerox copies; Form B—2 originals.

TYPE PERFECT ORIGINAL OF ABSTRACT HERE
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1. Full Name and Address of Author who will present paper:

Dr. David Innes
Temple University School of Dentistry
Department of Physiology and Biophysics
3223 N. Broad Street
Philadelphia, PA 19140

2. Mode of presentation:
- ☒ oral presentation only
- ☐ read by title acceptable
- ☐ poster presentation only
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3. Do you wish to withdraw your paper if it
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GROUP CLASSIFICATION

4.

- ☐ Behavioral Sciences
- ☐ Cariology
- ☐ Craniofacial Biology
- ☐ Dental Materials
- ☐ Microbiology, Immunology
- ☐ Mineralized Tissue
- ☐ Neuroscience
- ☐ Periodontal Research
- ☒ Pharmacology Therapeutics, Toxicology
- ☐ Prosthodontics
- ☐ Pulp Biology
- ☐ Salivary Research

SUBJECT CLASSIFICATION

5.

- ☐ Anatomy
- ☐ Biochemistry
- ☐ Cell Biology
- ☐ Chemistry
- ☐ Education
- ☐ Embryology
- ☐ Endocrinology
- ☐ Endodontics
- ☐ Enzymology
- ☐ Epidemiology-Biostatistics
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- ☐ Health Services
- ☐ Histology
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- ☐ Orthodontics
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- ☐ Preventive Dentistry
- ☐ Radiology, Radiobiology
- ☐ Restorative Dentistry
- ☐ Temporomandibular Joint
- ☐ Tissue Culture
- ☐ Ultrastructure

☐ Other _____

Effects of Acute Methyl Methacrylate Inhalation on Rat Brain Neuronal Activity.

D.L. INNES*, M.F. TANSY and J.S. MARTIN.
Temple Univ. Dental School, Philadelphia.

Emphasis has been placed in the Russian literature on the occurrence of central nervous system (CNS) disorders in workers exposed to methyl methacrylate (MMA) monomer vapor. Unfortunately, only a scanty amount of information is available in the Russian studies. Therefore, we decided to determine what CNS effects could be inferred to exist in rats which received acute exposure to this vapor. Nightly fasted adult male Sprague Dawley rats were anesthetized to a surgical plane with chloralose-urethan. Stainless steel bipolar microelectrodes, stereotaxically positioned into selected brain structures yielded continuous multi-unit recordings of ongoing electrical activity, while simultaneously exposing the animal to MMA vapor. A test session consisted of a 60 min exposure to 400 ppm of MMA in room air bracketed by 30 min rest periods. We have identified the lateral hypothalamus as a region where cells are found which are sensitive to MMA inhalation. Cells in the ventral hippocampus also responded to the MMA stimulus. In contrast, identical MMA stimulation of the parietal cortex, cerebellum, dorsal hippocampus, medial amygdala, ventral medial hypothalamus, anterior hypothalamus, septum, and mammillary body resulted in insignificant changes. It is concluded that acute respiratory tract exposures to MMA are associated with significant alterations in neuronal activity in at least two areas of the rat brain.

(Supported by NIOSH Grant OH-00740-01)

6. Reviewer's Rating:					7. Disposition:				
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ O	☐ P	☐ T	☐ R	☐ W

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FORM A
INTERNATIONAL ASSOCIATION FOR DENTAL RESEARCH
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ABSTRACTS MUST BE RECEIVED BY OCTOBER 16, 1979

Complete: Items 1-7 below and type abstract within box, following instructions on reverse side.
Submit: Form A — Original and 4 Xerox copies; Form B card — 1 original (complete blank 3x5 card for each co-author, in same style as Form B).

1. Full name and address of author who will present paper. David L. Innes, Ph.D.
Dept. of Physiology and Biophysics
Temple Univ. School of Dentistry
3223 North Broad Street
Philadelphia, PA 19140

2. I wish my paper considered for (check one) IADR (Japan) ☐ AADR (Los Angeles) ☒

3. (For NIDR Grantees ONLY.)
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- ☒ oral presentation only
- ☐ read by title acceptable
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- ☐ oral or poster mode acceptable

5. Do you wish to withdraw your paper if it is placed in a mode not of your choosing?
yes ☐ no ☒

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- ☐ Mineralized Tissue
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- ☐ Oral & Maxillofacial Surgery
- ☐ Periodontal Research
- ☒ Pharmacology, Therapeutics & Toxicology
- ☐ Prosthodontics
- ☐ Pulp Biology
- ☐ Salivary Research

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- ☐ Education
- ☐ Embryology
- ☐ Endocrinology
- ☐ Endodontics
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- ☐ Radiology, Radiobiology
- ☐ Restorative Dentistry
- ☐ Temporomandibular Joint
- ☐ Tissue Culture
- ☐ Ultrastructure

TYPE PERFECT ORIGINAL OF ABSTRACT HERE
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Methyl Methacrylate Vapor and Multi-Unit Activity in the Rat Brain. D.L. INNES* and M.F. TANSY. Temple University School of Dentistry, Philadelphia, PA

Last year we presented evidence demonstrating significant alterations in ongoing neuronal activity of two separate areas of the rat brain following acute exposure to 400 ppm of methyl methacrylate (MMA) vapor. We identified the lateral hypothalamus and ventral hippocampus as nuclear regions wherein the cellular response to the MMA stimulus was associated with a decreased rate of firing. These results led us to explore the effects of other gas concentrations to determine threshold exposures for these areas. Nightly fasted adult male Sprague Dawley rats were anesthetized to a surgical plane with chloralose-urethan. Stainless steel bipolar microelectrodes stereotaxically positioned into the cerebellum, parietal cortex, dorsal and ventral hippocampus, medial amygdala, septum, anterior, lateral and ventral medial hypothalamus, and mammillary body yielded continuous multi-unit recordings of ongoing electrical activity, while simultaneously exposing the animal to the MMA vapor. Test sessions consisted of 60 min exposures to either 800, 400, 200, 100 or 50 ppm of MMA in air bracketed by 30 min rest periods. We observed significantly reduced activities in the lateral hypothalamus and ventral hippocampus at exposures as low as 100 ppm but not at 50 ppm. None of the other areas showed significant changes in activity at any concentration employed. It is concluded that the threshold exposure concentration for this effect is the same as or less than the current threshold limit value (TLV) for methyl methacrylate monomer vapor.

Supported by NIOSH Grant OH-00740-02

8. Reviewer's Ratings:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

9. Disposition:
☐ O ☐ P ☐ T ☐ R ☐ W