

A STUDY OF THE POSSIBLE PUBLIC HEALTH HAZARDS
ARISING FROM THE USE OF TETRAETHYL LEAD IN THE AUTOMOBILE

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The Laboratory of Industrial Hygiene, Department of Physiology, Columbia University, was invited by the Medical Committee of the Ethyl Gasoline Corporation to make an independent study of the possible hazards to the public from the proposed use of tetra ethyl lead in the gasoline sold to automobilists.

Tetra ethyl lead is a colorless liquid with a specific gravity of 1.62 at 15 degrees C., boiling at 200 degrees C., but not without decomposition. It is a lipoid solvent, attacks rubber and is insoluble in water. It is due to the fact that it is a lipoid solvent that makes it a hazard through skin absorption. When exposed to sunlight or evaporated it decomposes and forms as one of its decomposition products tri-ethyl lead, - another poisonous compound whose properties have been studied by Harnack. When used in the automobile it is added to gasoline, together with an organic halide in the proportion of 1000 parts of gasoline to one part of the lead compound, which mixture is known to the trade as ethyl gasoline.

As the Bureau of Mines had already been studying the possible hazards to the public from exhaust gases from engines using this ethyl gasoline, the Medical Committee suggested that Columbia University confine their efforts to the following possible hazards: -

- (1) The possible hazard to the garage man who might get a few drops of the concentrated material on his clothes or person from time to time as he was adding the lead compound to the gasoline at the Service Station.
- (2) The possible hazard that might arise from splashing ethyl gaso-

line (1000 to 1 mixture) on the person; from cleaning the hands or clothes by the mechanic or housewife: in adjusting the carbureter or cleaning out the gas line or tank, etc.

(3) The possible danger from the inhalation of ethyl gasoline fumes from spillage in the garage and other places where vaporization may take place.

Before our experiments were productive of results, an experimental plant of the Standard Oil Company of New Jersey, at Bayway, while engaged in a study for the improvement in the method of manufacturing tetra ethyl lead, had an unfortunate experience. In spite of precaution taken by the manufacturer, a number of men became poisoned at one time and were placed under observation at the Reconstruction Hospital, New York City. One man died before the men were sent to the hospital. The symptoms of the worst cases were those described by several writers in cases of acute lead poisoning and were very similar to those produced by ethyl alcohol. In the severe cases there were indications of profound cerebral disturbances. The victim suffered from persistent insomnia and became delusional, extraordinarily restless and talkative. There was an exaggerated movement of all the muscles of the body. The patient became maniacal and may have died in exhaustion. Four of the men transferred to the hospital died within a few days. The rest of the men were discharged from the hospital after receiving the proper treatment.

While studying these cases at the Reconstruction Hospital, the excreta of 29 of the patients were examined and lead was found in the stools of 18 men. Stippled cells were found in the blood of nine out of twelve men examined by this laboratory. We could not detect any lead in sweat collected from a number of the men subjected to thermal baths. Tests were also made on the skin with ammonium sulphide but likewise gave no reaction. Several samples

of spinal fluid gave negative results as well.

The report of the Chief Medical Examiner of New York City of the autopsies performed on the four men who died at the hospital, reveals no special gross pathological findings. Without a chemical analysis or knowledge as to where the men had worked one would have been unable to say that lead was the cause of their death. This of course is in agreement with our past knowledge as to the pathological or histological findings in lead cases.

The autopsies determined the cause of death "pending chemical examination and investigation as hemorrhagic, broncho-pneumonia, visceral congestion" in two cases, "hemorrhagic broncho-pneumonia, secondary anemia" in the third and fourth "general visceral congestion."

We have given these data as an aid to a better understanding of our own findings.

The Ethyl Gasoline Corporation proposed to remove any possible Public Health Hazard from the concentrated tetra ethyl lead by delivering only the 1000 to 1 mixture to the filling station. It is thought to lessen the possible hazard through the skin absorption when handling the dilute mixture by adding a red dye to the mixture. This prevents the housewife from cleaning her gloves or clothes with gasoline drawn from the gas tank of her husband's automobile.

ANIMAL EXPERIMENTS

Animals:

Matured rabbits, guinea pigs, goats, rats and monkeys were used in this work. The animals were kept under observation for a period of time before using and their weights and temperatures carefully noted during the whole series of experiments. The blood of the rabbits and goats was carefully examined for red, white and differential counts, as well as for stippled cells. The control animals were kept from the treated animals so that they would not have a chance to accumulate lead in any way. Outside of this precaution all of the animals were treated in the same manner. Samples of feces were collected from time to time and examined for lead.

Methods of Examination:

Three stains were used in examining the blood for stippled cells, - Wright, Gilbert and a modification of the Leishman's stain suggested by the Ontario Report on Lead.

Lead:

The bodies were burnt at a low temperature over a gas flame so as to avoid any volatilization of lead. The chromate method described by Fairhall was used in the actual determination of lead.

Dosing of Animals in the Skin Absorption Tests:

We determined at the beginning of our work that a man would have approximately ten cc left on his hands after washing them and before drying them on waste or towel. Using this as a basis we dosed our animals in the same proportion, taking the weight for man as 70 kilos. We felt that this was as near as we could come to duplicating an industrial condition. In the case of a spillage the exposure would be much greater. However if lead storage took

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place with our approximately small daily exposure one may be sure of a greater absorption with the larger exposure.

The ethyl gasoline was allowed to flow slowly from a small pipette on to the uninjured skin by pushing the hair aside where possible. When shaving was necessary, the animal was not dosed on the shaven area for several days. The gasoline was applied to various parts of the body with the exception of the goats which were dosed either on the neck or side. Care was taken never to apply the gasoline to any broken skin. The dosing of the animals took place daily except Sundays and holidays except when feces were being collected.

At the beginning of our work, we were inclined to think that the actual poisoning took place through ingestion or inhalation. Rabbits and guinea pigs have the habit of cleaning their fur with the tongue, and not only can they be seen doing this to their own bodies but to other animals of the same species. We tried to overcome this by placing jackets on the animals, but these jackets got torn and observation led one to the opinion that it interfered with the physiological activities of the animal. Normal animals died without receiving any exposure. It was for this reason that we decided to use goats as well as the smaller animals in our work. They are a hardy animal and so far as we have observed have no tendency to lick themselves.

To determine whether absorption really did take place through the skin and not by ingestion or inhalation we made the following tests:-
Three cats at different times were anesthetized with ether. Tracheotomy was performed and a canula placed in the carotid so as to observe the blood pressure and respiration. The tube from the trachea was led away from the body in such a way that there was no chance for the animal to inhale any of the fumes. To further safeguard any accidental breathing in of any tetra ethyl lead fumes, an exhaust fan was placed near the body to draw off any fumes from

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the head. In addition an electric fan was placed near the head of the cat as a further precaution. 6 cc of concentrated tetra ethyl lead was allowed to flow from a pipette on to the clipped abdomen and a record taken on the kymograph so that any change in blood pressure or respiration rate could be noted. One of the cats died within eleven minutes while the other two lived an hour and two hours respectively. As far as our records show there does not seem to be any change in the blood pressure or respiration rate. As soon as our cats died the skins were washed thoroughly with alcohol to remove any tetra ethyl lead that might still remain on it. The cat was then quickly skinned and the abdomen opened up for examination. Blisters were observed in each case all through the abdominal region and the intestine had a peculiar bluish hue. The odor of the chemical was quite distinct when the abdominal cavity was first opened. After this gross examination the whole body with the exception of the skin was burnt and the lead contents determined. The average lead content of the three cats used in these experiments was found to be 0.651 grams of lead. This experiment would seem to indicate that there is no doubt that this lead compound is quickly absorbed through the skin and if by any chance any should get on the skin it must be immediately washed off with kerosene and green soap. Water and ordinary soap will not remove it. The ability of the tetra ethyl lead compound to enter the body through the skin readily brings us face to face with a comparatively new lead hazard.

It should be emphasized that the above experiments were made with the concentrated tetra ethyl lead, and not with the 1000 to 1 dilution.

Hazard from Skin Contact:

This part of the research has to do with the possible hazard that may exist from the dilute gasoline coming in contact with the skin and a subsequent absorption into the body of the minute quantity of the lead compound present in

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the gasoline.

Rabbits, guinea pigs and goats were used in this part of the study.

Summary of Rabbit Experiments:

Each animal received 0.30 cc of a 1000 parts of gasoline to 1 part of tetra ethyl lead mixture. It was applied to the unbroken skin by means of a small pipette, applied practically daily until the animal died. The number of exposures that the animal underwent varied from 6 to 187.

28 animals which have died:

Temperature	Initial 38.9 deg. C.	Final 38.8 deg. C.
Weight	" 2.111 kilos	" 2.03 kilos
Red Blood Count	" 4.87	" 4.86

Stippled cells were found in the blood of 14 of the rabbits that have died.

The two rabbits dying after receiving but 6 and 13 doses showed only traces of lead when they were burnt and their carcasses were examined for lead. An average of 2.10 mgs of lead per kilos of body weight was found in the bodies of examined animals. The quantity of lead accumulating in the body does not always follow the number of exposures that the animals were subject to. But there seemed to be a tendency to have an increased lead storage with the greater exposure.

Excretion:

The average rate of excretion as shown by frequent examination of the feces seemed to indicate that it was approximately 0.044 mgs per 24 hours and it does not apparently increase with the greater storage of lead.

Generally a few days before the animal died it became quiet and hunched up as if suffering from colic. Four of the rabbits showed tremors and spasms before death. One rabbit receiving 185 applications became completely paralyzed in the hind quarters several days before death. This animal showed

4.90 mg of lead per kilo of body weight. Several of the rabbits aborted but the fetus was not examined for lead.

Autopsy:

An autopsy was performed on each animal that died and revealed nothing more than was found in the control animals when they were killed or died except that there was the consistent presence of a white blood clot in the right auricle of the leaded animals. This was also observed in several supposedly normal animals. The ante mortem clot is usually accounted for by a slowing down of the circulation. If this is the correct explanation it will corroborate what has been observed on men who have been exposed to the compound, - namely a lower blood pressure. One man in whose 24 hour urine sample we had found 12 mgs of lead had a systolic pressure of 90.

Experiments on Guinea Pigs:

10 pigs were used in this part of the experiment. They received 0.10 cc of the 1000 to 1 mixture on their unbroken skin daily until death. The number of exposures varied from 10 to 46.

Weight: Initial 448.8 Final 394.3

The average lead per kilo body weight was found to be 1.07 mgs. Three pigs had convulsions and tremors before death.

Experiments on Goats:

7 goats were given 2 cc of the 1000 to 1 mixture daily. These goats are still alive. Their exposures have varied from 79 to 107. Two of these goats have aborted and an analysis of the fetus showed that it contained mgs. of lead. Stippled cells were not found in the blood for over two months but have increased in numbers since. One of the goats which has received 107 doses of the dilute solution shows a marked muscular weakness in the hind quarters. Another goat is beginning to show the same effect.

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Two goats were given 1 cc of the concentrated tetra ethyl lead daily for approximately two months. Both of these goats have aborted. One died after receiving 60 exposures. It had a marked weakness in the hind quarters for several days before it died. The day that it died it was unable to stand or use its hind limbs, and it spent the whole day crying. An analysis of the various organs showed the lead to be distributed in the following manner:

Brain	Lungs	Liver	Muscle
Heart	Kidney	Bone	

Both of the goats receiving the concentrated lead compound remained quiet and hunched up as if in pain most of the time.

The goats being treated with the 1000 to 1 mixture are apparently excreting 0.10 mg of lead each twenty-four hours.

The goats receiving the concentrated tetra ethyl lead apparently excreted 0.56 mgs each twenty four hours.

Hazard from Vapors:

The gas chamber is a room containing approximately 180 cubic feet of air space. It is ventilated by means of a fan delivering air near the floor. The air is removed by means of a flue in the ceiling. The air in the chamber is changed once in ten minutes or six times per hour. The air contains approximately 0.03 mgs of lead on the average. This is regulated by bubbling air through an ethyl gasoline mixture at the proper rate to accomplish this object. It is hard to duplicate the actual conditions that may be present around filling stations or the garage. However, we did not try to evaporate the last portions of the gasoline in the bottle. This was done because it has been observed that there is a concentration of the tetra ethyl lead as lighter gasoline evaporated. The amount of lead in the evaporated gasoline varies as the lighter portions of the gasoline are evaporated. In the garage this same condition

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would be true. We made some experiments by spilling some ethyl gasoline on boards and found that it practically all evaporated in the natural air movement. If, as has been claimed, the tetra ethyl lead is not evaporated with the gasoline then the garage man will be exposed to the fumes of the concentrated tetra ethyl lead. The tetra ethyl lead also decomposes under certain conditions and tri-ethyl lead crystals are formed which, as Harnack has shown, is very poisonous.

Goats, rabbits, guinea pigs, pigeons and rats are being exposed in the gas chamber, for an average of four hours a day. Care is taken that no food or other material that might be gnawed is present. The only way that lead can get into the body is through the respiratory tract unless some vapor should be deposited in their fur which is highly improbable. The rats seem more sensitive than the rest of our experimental animals. The animals have received exposures varying from 16 hours to 266 hours. The rabbits and goats that have been exposed after a time begin to show stippled cells in their blood.

An examination of the carcass of 38 animals showed the lead contents to be 5.17 mgs of lead per kilo of body weight.

The animal usually became quiet and hunched up for several days before dying. An autopsy reveals no special findings.

One of the guinea pigs gave birth to two pigs. Neither the mother nor her young were exposed to lead after their birth. The young pigs lived seven days, then had convulsions and died. An analysis showed that their bodies contained 0.60 mgs and 0.68 mgs respectively.

Human Observation:

Two persons who have followed the work since the beginning and who have taken precautions knowing the poisonous nature of the compound, have stored

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lead as shown by an examination of the urine and feces:

	<u>Feces</u>	<u>Urine</u>
24 Hr. Sample	0.76 mg	0.08 0.14
24 Hr. Sample	0.42	0.07

It is interesting to note that neither one of these persons noted any special symptoms, and in fact one of them had passed two insurance examinations within a month. They both speak of wakefulness at night, irrational dreams, nervousness, and a general feeling of malaise which expresses itself in a general lack of "pep". Any doctor treating them would have laid it to a run down condition, needing a little tonic, etc.

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As ethyl gasoline cannot be sold in New York City, it has been necessary for us to purchase the gasoline (Standard) at a filling station and to add the tetra ethyl lead to it ourselves. We keep the bottle containing the concentrated material on the roof outside of the experimental animal house. The concentrated tetra ethyl lead is measured out with a pipette and added to the gasoline - all of this is done out of doors, and the exposure to the fumes from the concentrated material is practically nil. Leather gloves are worn when handling any container. Enough of the 1000 to 1 mixture is made up to last approximately two weeks.

Care is taken in dosing the animals never to get any of the material on the hand. If at rare intervals any did get on the finger, the hands were washed immediately. The only probable way that the lead could have gotten into the system is by inhalation of the diluted fumes. The solution is handled in a pipette which is stuck into the bottle containing the solution. When the solution has flowed into the pipette, a rubber tube at the upper end is squeez-

ed together, thus retaining the solution in the pipette. Then the pipette is placed on the skin of the animal and the pressure on the rubber rubbing released, permitting the solution to flow slowly on to the skin.

We have in the past dosed some animals with concentrated material, but the exposure wouldn't amount to more than two minutes a day and the operation was carried out under practically outdoor conditions. This exposure would not be more than would come from the concentrated solution left on the floor of a garage, if the contention of certain parties is correct that practically only gasoline evaporates. We determined at the beginning of our investigation that approximately 5% or 100 cc of a concentrated tetra ethyl lead solution by weight in a 250 cc beaker left open out of doors would evaporate in a week. Unfortunately in these tests, we did not make any lead determinations. The tests were carried out while we were still skeptical as to whether there was much danger except from ingestion.

SUMMARY

Our experiments indicate apparently that there is no doubt that animals exposed to skin application of ethyl gasoline will store lead. The rate of excretion does not equal the rate of absorption. This is entirely in agreement with all medical experience. We are not prepared to say that all of the animals that died did so because of the lead. The thing to bear in mind is that there is no doubt that a storage of lead takes place under exposure. Lead stored in the body constitutes a potential lead poisoning. There is one thing, that we have noticed at various times, and that is, if for any reason we do not expose the animal which may appear sick for several days, the animal will show a marked improvement. This is again in line with medical experience in cases where patients have been exposed to lead. One cannot but feel on

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account of this observation, that their condition before the rest was due to the lead exposure.

The same observations that have been made about animals receiving skin applications, can be made on the animals that were exposed to fumes of the dilute ethyl gasoline. It is of significance that there is a continuous storage of lead taking place in the animals no matter whether it is by absorption through the skin or by inhalation. What is of special significance or seems to be so to us, is the fact that the animals in the gas chamber seem to show the effects quicker than through skin application. Of course one might expect this from one's knowledge of physiology. It also confirms the findings at Harvard. The dilution does not seem to make any difference except for the longer time necessary to accumulate the same quantity of lead.

Whether man will receive the same exposure that our animals have is a matter to be investigated. The University was not asked to determine this question. From the two human cases referred to, it would seem reasonable to expect that if the exposures were the same as those of the animals, that man would store lead the same way the animals did.

In order to determine whether a public health hazard does exist in the use of ethyl gasoline, I would make a suggestion that the Surgeon General appoint a Committee who will select certain filling stations and garages where ethyl gasoline is used generally. That the dust on the floors and walks of the garages be collected from time to time and the lead contents determined. Care should be taken not to change the general habits of the men around these places as to cleaning the floors, etc. A group of men in these places should be examined at regular periods over a sufficient length of time to give any symptoms a chance to develop. The study should include an examination of the

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stools and urine. This is especially necessary when one refers to the two cases at Columbia University and their apparent lack of any symptoms that the ordinary doctor would have associated with lead poisoning.

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