Absorption and Excretion of Mercury in Man

IV. Tolerance to Mercury

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Introduction

It is a matter of ordinary prudence that, when the amount of a toxic agent which can safely be tolerated by humans is unknown, any possible error in establishing threshold limits be on the side of caution. On the other hand, the imposition of limits which are unnecessarily severe can result in undue hardship to industry and may tend to discredit the entire threshold limit concept.

Of the 256 chemicals for which threshold limit (TL) documentation has been compiled [1] an overwhelming majority have been assigned TL values on the basis of animal experiments alone or combined with meager human observations. Mercury is exceptional in that it is one of very few materials for which the TL is based entirely on human studies.

It is not the purpose of this report to review all published data on human exposure to mercury. A comprehensive review has recently been published.[2] In this paper selected reports dealing with human tolerance to mercury will be discussed, and results of human observations spanning a period of 21 years will be presented. Animal experiments will be considered in subsequent articles.

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Inorganic Mercury

The current TL for inorganic mercury of 0.1 mg/cu meter is based on studies in the felt hat industry made by the US Public Health Service, the results of which were published in 1941,[3] and on the unpublished data communicated to the Committee on Threshold Limits of the American Conference of Governmental Industrial Hygienists (ACGIH).[1] In the felt hat study, 3 out of 66 men with mercury exposure of less than 0.08 mg/cu meter of air were classified as "borderline" cases of poisoning and 15 out of 127 with exposure of 0.08-0.15 mg/cu meter as "borderline" or "first stage." It is stated in the report "that the lowest atmospheric concentration for which a case of mercurialism was recorded was 1.0 mg Hg per 10 m^3 of air," or 0.1 mg per cubic meter.

Another significant study of mercury exposure in the felt hat industry was made by the Division of Industrial Hygiene of the New York State Department of Labor in 1937. For some unknown reason the results were not published until 1948 and 1949.[4,5] This study included environmental data and comprehensive physical and laboratory examinations on 213 persons. There were 35 subjects whose occupational exposure to mercury in air was less than 0.1 mg/cu meter, and of these there were four who were diagnosed as having mercury poisoning and an additional ten classified as "borderline." The authors point out that in the hat industry (at that time) there was ample opportunity for the absorption of mercury through the skin because of the use of mercury nitrate in the "carroting" process and the wet nature of the early stages of hat making. Bidstrup [6] has reported evidence of poisoning in a meter-repair shop in which the atmospheric mercury never was found to exceed 0.065 mg cu/meter.

Buckell [7] found "up to 10 times as much mercury in a day as could possibly be absorbed through the atmosphere" in the urine of 72 men in a thermometer workshop, and he attributed this to skin absorption. He recommends that atmospheric mercury never be permitted to exceed 0.075 mg/cu meter.

Prior to the study cited above [3] which apparently has served as the principal basis for the present TL for inorganic mercury, the US Public Health Service had also investigated the hatters' fur-cutting industry. The work was done in 1935 and published in 1937.[8] In this study six of 107 persons (5.6%) exposed to mercury vapor in concentrations of less than 0.1 mg/cu meter were diagnosed as having mercurialism.

The adoption of 0.1 mg/cu meter as the TL for inorganic mercury is reminiscent of the original TL for benzene of 100 ppm which was in vogue for a number of years even though the work on which it was based showed injury to the blood at that level.[9] In the case of inorganic mercury it is by no means rare to find reports of poisoning associated with exposures below or very slightly above the TL of the ACGIH. On the other hand Kleinfeld et al [10] have reported studies which include a group of 15 workers who were exposed to average mercury concentrations of 0.201 mg/cu meter (range 0.080-0.400) for more than two years with no evidence of intoxication. The exposure was to inorganic mercury.

Organic Mercury

Tolerances in the form of TL values are given for about two dozen metals in the ACGIH list.[1] Mercury is the only metal which receives the special treatment of having one TL for inorganic and another for organic compounds, the latter being one tenth of the former. (It is interesting that no such distinction has been made in the case of lead, particularly since Elkins [11] has proposed a TL of 0.1 mg/cu meter and Kehoe [12] a TL of 0.075 mg/cu meter for organic lead compounds.) Reported human observations on the toxicity of certain organic mercurials, particularly the alkyls, seems to justify establishing separate TL's for inorganic and organic mercury. Apparent differences between alkyl and phenyl mercurials will be discussed below.

The TL of 0.01 mg/cu meter for organic compounds of mercury as given by the ACGIH is based on five cases of methyl mercury poisoning reported by Ahlmark in 1948 [13] and eight cases of poisoning due to alkyl mercury compounds reported by Lundgren and Swensson in 1949.[14] Neither of these reports contains any data on atmospheric concentrations of mercury. Ahlmark arbitrarily suggests that "a percentage higher than 0.01 mg. per cubic meter of methyl mercury compounds should not be allowed." Presumably he means 0.01 mg of methyl mercury compounds per cubic meter of air. Lundgren and Swensson say that "it is impossible to define a maximum allowable air concentration of mercury." The ACGIH, therefore, must base its TL on Ahlmark's unsubstantiated opinion. The ACGIH quotes from the painstaking studies of Dinman, Evans, and Linch [15] which cast serious doubt on the validity of the TL of 0.01 mg/cu meter, but choose to retain this figure "because newer types of organic mercurials of possibly greater toxicity than those studied by Dinman are appearing." Dinman, incidentally, followed 20 men closely over a period of six years with urinalyses for mercury and physical examinations performed at least once a month and air studies done daily. Exposure was to ethyl mercury chloride and phosphate, and ethyl and phenyl mercury acetate with atmospheric concentrations consistently between 0.01 mg/cu meter and 0.1 mg/cu meter. There was no evidence of intoxication.

Observations similar to those of Dinman have been reported by Massmann in Germany.[16] A group of 23 men were exposed to

TABLE 1.—*Summary of Findings in Plant X*

Date	No. of Men Examined	Abnormal Signs or Symptoms	Hg in Urine, Range *	Hg in Blood, Range †	Hg in Air, Range ‡
December, 1948	19	None	130-3,169	—	—
April, 1949	—	—	—	—	150-440
April, 1959	12	None	272-2,550	8-51.0	194-246
March, 1961	32	None	1-1,800	0-32.0	2-560
March, 1962	29	None	0-2,887	0-40.0	100-2,390
October, 1962	39	None	8-1,350	0-24.0	—
December, 1962	—	—	—	—	60-650

* Micrograms Hg per liter of urine.
† Micrograms Hg per 100 ml of blood.
‡ Micrograms total Hg per cubic meter of air.

phenyl mercury pyrocatechin and phenyl mercuric acetate for periods up to six years, the air concentrations being from 0.24 to 3.20 mg Hg/cu meter. One man excreted mercury at the rate of 6.0 mg per liter! Others had values between 1-4 mg Hg/liter. No cases of intoxication were found.

Our Observations

It has been possible to perform fairly detailed studies in two plants which process a variety of mercurials. These plants shall be designated plant X and plant Y. The studies included histories and physical examinations designed to detect any evidence of mercury poisoning, as well as mercury determinations in urine and blood. The urines were also tested for specific gravity, sugar, and albumin.

A summary of the studies done in plant X is given in Table 1. The first observations were made in December, 1948, and April, 1949. A detailed account of the findings was published in 1949.[17] At that time the plant was engaged in manufacturing oxides and chlorides of mercury and in purifying mercury by redistillation; in other words, only inorganic mercurials were involved. It is obvious from the air and urine figures in Table 1 that a substantial exposure existed. Just prior to the time of these studies there had been a case of severe nephrosis in an employee who worked at a mercury recovery operation in the open air.[18]

Between 1949 and 1959 the work at plant X changed in that organic mercurials had become the principal products. Exposure levels have remained high. Many of the employees of 1948 are still working at plant X. One man whose urine showed 3.69 mg of mercury per liter in 1948 had 1.80 mg/liter in 1961 and 2.88 mg/liter in 1962. He has no clinical signs of intoxication.

Although no detailed studies were performed between 1949 and 1959, there is no reason to believe that environmental conditions were very much different during that period from what they were before and after. Periodic physical examinations were done semiannually by a part-time local physician. No evidence of intoxication was found.

The story in plant Y is similar to that of plant X except that the first observations were made in 1941. At that time plant Y also was concerned almost entirely with inorganic mercurials. Over the years their activities changed so that by 1961 the production of organics had greatly increased. From 1953 to 1958 periodic physical examinations and urine mercury determinations were performed by a group which is no longer associated with the plant, but the records have been available for review. A summary of the findings in plant Y is given in Table 2.

It is apparent that in plant Y as well as in plant X there has been significant exposure to various forms of mercury for many years. Improved industrial hygiene practices have been introduced, but substantial exposures still exist, and probably did throughout the years, as evidenced by the urine mercury levels. The situation between 1941 and 1953 is, of course, not definitely known.

TABLE 2.—*Summary of Findings in Plant Y*

Date	No. of Men Examined	Abnormal Signs or Symptoms	Hg in Urine, Range *	Hg in Blood, Range †	Hg in Air, Range ‡
June, 1941	—	—	—	—	80-2,400
1953 §	21	None	28-672	—	—
1954 §	23	None	26-660	—	—
1955 §	20	None	40-1,020	—	—
1956 §	21	None	10-270	—	—
1957 §	13	None	14-480	—	—
1958 §	23	None	0-730	—	—
May, 1961	28	None	22-2,325	0-33.0	200-1,200
January, 1962	34	None	10-952	1.5-49.6	—
August, 1962	35	None	0-2,287	0-38.7	40-970

* Micrograms Hg per liter of urine.
† Micrograms Hg per 100 ml of blood.
‡ Micrograms Hg per cubic meter of air.
§ Examinations by other observers.

Urinary Mercury in Relation to Tolerance

In the absence of any pathognomonic symptom, sign, or laboratory test which will indicate early intoxication from mercury it has been customary to rely upon urinary mercury as a guide in medical control of mercury poisoning.[6,13,15] Theoretically, at least, this can be justified on the basis that, in general, high exposures lead to high levels of mercury in urine as well as to high frequency of intoxication.[3-8] On the other hand, it has been shown that in individual cases high values of mercury in urine frequently occur without evidence of poisoning and that poisoning can occur in association with relatively low levels of urinary mercury.[3-5,7] The data given in Tables 1 and 2 confirm the fact that urinary mercury even in the milligram range is by no means always associated with intoxication. The statement made by Bidstrup and associates [6] that the excretion of more than 300μg of mercury in 24 hours is usually accompanied by symptoms and signs of chronic mercury poisoning has unfortunately been misinterpreted as meaning that excretion of that amount of mercury is in itself proof of mercury poisoning. A careful reading of Bidstrup's entire article (not just the summary) shows that the 300μg figure was used as confirmatory evidence in questionable cases and not as absolute proof of intoxication.

Another feature which detracts from the usefulness of urinary mercury levels as an index of tolerance is the extent to which these levels can fluctuate from day to day. Buckell [7] found that in the space of six successive days the excretion of mercury in urine in a thermometer marker varied from 96μg to 1,000μg in 24 hours. We have found similar, but less extreme, daily fluctuations in three men in plant X.

In 1955 Stokinger [19] introduced a concept which he calls "Biological Threshold Limits" in which an attempt is made to relate the concentration of air contaminants or metabolites in urine to tolerance to the respective contaminants. The general validity of this interesting idea, as predicted by Stokinger, has not been widely established. The biological threshold limit he gives for mercury in urine of 0.25 mg/liter, although close to Bidstrup's 0.30 mg/liter, certainly does not represent a limit above which toxic manifestations will occur with any degree of regularity.

Mercury in Blood

Extensive studies of mercury levels in the blood in humans are of fairly recent date.[20,21]

It had been hoped that the determination of mercury in blood might be useful in establishing tolerance to occupational exposure, but results so far have been disappointing.

Tolerance to Mercurial Drugs

While experience from clinical medicine and pharmacology may not be directly applicable to problems of tolerances to industrial chemicals, it is none the less true that useful information may be found in the medical literature. Mercury is a case in point.

A complete review of toxicological effects from the use or misuse of mercurial medicaments would be a formidable undertaking, far beyond the limited scope of the present paper. Coverage of the older literature can be found in some of the standard textbooks of pharmacology, particularly that of Sollmann.[22] A symposium on mercury and its compounds held by the New York Academy of Sciences a few years ago provides a rich source of information, particularly on organomercurial diuretics.[23] There are literally hundreds of articles containing toxicological information on mercury that have been published in journals which ordinarily do not come to the attention of persons in the industrial hygiene field. There is no reason why this type of data should be eschewed in establishing TL values for mercury, as well as for other chemicals, even though routes of absorption are different and interpretation may be difficult. Similar difficulties have not ruled out the use of data obtained from animal experiments.

One striking example of tolerance to mercury may be cited. Leff and Nussbaum have reported a series of 48 patients treated with mercurial diuretics for four years.[24] These patients received total mercury ranging from 6,240 mg to 78,560 mg with no evidence of mercurial toxicity. These figures prompt a small flight of fancy.

It is stated that a man at work inhales about 10 cu meters of air in an eight-hour day. If mercury were present in the air in a concentration of 0.1 mg per cubic meter, the total daily inhalation would be 1 mg of mercury. Assuming 250 work days per year and 95% to 100% absorption of inhaled mercury, as found by Shepherd,[25] the total absorption would be 250 mg Hg per year or 1,000 mg in four years. The mercury in diuretics is organic, for which the TL is 0.01 mg/cu meter. Following this line of reasoning (or speculation) it is obvious that at least some forms of organomercurials can be tolerated by some humans in amounts far in excess of what could be absorbed if the TL is applied.

Comment

As stated in the introduction, the purpose of this paper has been to review some of the published data on tolerance to mercury and to report some previously unpublished data. Obviously there is an additional purpose, namely, to stimulate discussion on the present mercury TL values and perhaps even to prompt a revision of these. This has already been suggested by Axelsson and Friberg.[26]

A few cogent questions might be asked, such as:

1. Is the present TL for inorganic mercury too high, too low, or just right? The data upon which it is based strongly suggest that it is too high, but perhaps better data are now available.
2. Is the present TL for organic mercury too restrictive, too permissive, or just right? It has been shown that this value is based on very meager evidence.
3. Is it reasonable to have a single TL value for *all* organomercurials? There is strong evidence that some of these compounds, the mercurial diuretics, for example, have a relatively low order of toxicity. The same can be said for some of the phenyl mercury compounds. The alkyl mercurials appear to fall into a different category.
4. How can skin absorption be given appropriate consideration in establishing TL values for mercury?
5. What weight should be given to medical and pharmacological data in arriving at TL values?

In the case of mercury, unlike that of most industrial chemicals, a considerable amount of data on human tolerance is available. As a result it should be possible to establish a TL value that has a fairly sound scientific basis. It may be, however, that before this can be done it will be necessary to find a more delicate test for toxicity than is now in use. Recent developments in enzymology, as suggested by Dinman [15] and Stokinger,[27] may hold the answer.

Summary

The bases for present threshold limit (TL) values for inorganic and organic mercury have been critically examined and found to have inherent weaknesses.

Human observations spanning a period of 21 years suggest that tolerance to some forms

of mercury may be greater than has been believed.

The propriety of a single TL for all organomercurials is questioned.

The use of data from clinical medicine and pharmacology in arriving at TL values is suggested.

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