Lower fiducial limit of urinary metabolite level as an index of excessive exposure to industrial chemicals

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Imamura, T., and Ikeda, M. (1973). British Journal of Industrial Medicine, 30, 289-292. Lower fiducial limit of urinary metabolite level as an index of excessive exposure to industrial chemicals. Utilization of the lower fiducial limit (P = 0.10), rather than the mean, as an index of excessive exposure to industrial chemicals is discussed. Cases of exposure to trichloroethylene, phenol, and toluene are used to illustrate this approach.

Since the early studies by Elkins (1954 and 1959), increasing attention has been paid to the quantitative relationship between intensity of exposure of humans to an industrial toxic agent and the level of the agent (or a metabolite derived therefrom) in an appropriate biological sample, and the concept of 'biological threshold limit' has been proposed (Elkins, 1967).

One of the main points to be discussed herein is determination of a screening level for the concentration of the metabolite in the biological specimen so that the factory worker may be protected from excessive exposure above the (atmospheric) threshold limit value (TLV). A proposal is made and substantiated as to utilization of the lower fiducial limit, rather than the mean, as a screening level. Examples of practical procedures are outlined.

Materials and methods
Previously reported data on the quantitative relationship between the levels of three industrial agents in the air of workrooms and the concentration of corresponding metabolites in the urine of workers exposed have been utilized, namely, toluene exposure v hippuric acid excretion (Ikeda and Ohtsuji, 1969a), environmental phenol v urinary total (free + conjugated) phenols (Ohtsuji and Ikeda, 1972), and trichloroethylene in air v total trichloro-compounds in urine (Ikeda, Ohtsuji, Imamura, and Komoike, 1972). The normal, i.e., non-exposed values were also reported (Ikeda and Ohtsuji, 1969b). The surveys in these studies were carried out in spring and autumn. Spot urine samples were collected from male workers at around 3 p.m. In some instances the metabolite concentration was corrected for either specific gravity of urine of 1.016 (Buchwald, 1964) or creatinine concentration (Jackson, 1966). The means and the fiducial limits of variations were calculated on the assumption that a log-normal distribution is applicable (Heath, 1967). Regression lines were fitted by the least square method.

Results
Results from the factory surveys have been schematically depicted in Figure 1. The horizontal and vertical axes represent atmospheric concentration of the toxic agent and urinary level of the metabolite, respectively. The mean metabolite level increases as a linear function of the vapour concentration with an expanding range of variation. Intercepts of the vertical axis by the lines for fiducial ranges give the upper and lower limits of the normal value. The mean and fiducial ranges of the urinary metabolite levels corresponding to the (atmospheric) TLV can be obtained at the intersection of the vertical line passing through the TLV on the horizontal axis and the respective regression lines of means and the fiducial ranges.
Survey data of factories using trichloroethylene, phenol or toluene were rearranged in accordance with this procedure, and the results are summarized in the Table. The probability of 0·10 is selected for the fiducial limit of the exposed value, so that 5% of the workers exposed to the TLV value of the compound will have metabolite concentrations below the lower fiducial limit. The screening level of total trichloro-compounds after trichloroethylene exposure at the TLV is more than 100 times higher than the maximum of the normal values, indicating that workers exposed at the TLV can be clearly separated from those non-exposed. This applies also to the subjects exposed to phenol vapour at the TLV. Urinary total phenols were measured, with the rate of the lower limit (P = 0·10) of the exposed value over the upper normal limit (P = 0·10) being approximately 5. In the case of toluene exposure, the upper normal limit is approximately 1 g/litre of urine or 1 g/g creatinine while the lower fiducial limit of the TLV-exposed value is between 1 and 2, indicating that separation of the exposed from the non-exposed can hardly be done regarding urinalysis for hippuric acid. It is clear from the comparison of the three cases in the Table that the reliability of the screening level depends on the ratio between the normal value and the TLV-exposed value as well as on the ranges of variation of the two values.

**Discussion**

The screening level may be determined (1) from the relation between the signs and symptoms of the factory workers exposed to the toxic agent and the level of the agent (or a metabolite(s) derived therefrom) in biological specimens (Ahlmak and Forssman, 1951) as in the (atmospheric) TLV, or (2) as the level of the agent (or a metabolite(s)) in the biological specimens obtained from the factory workers exposed to the agent at the TLV. The significance of the excretion rate in relation to the body burden after repeated exposures was recently discussed by Roach (1966), who suggested the advantage of factory surveys and limitation of experimental exposure as a simulation study especially when an agent with a slow excretion rate is to be examined. The biological half-life values of the three agents under study have been reported (Ikeda and Imamura, 1972; Sherwood, 1972). A number of studies, based on the second principle described above, were performed on the factory workers to determine screening levels in relation to the index of excessive exposure to organic solvent vapours (Walkley, Pagnotto, and Elkins, 1961; Ogata, Sugiyama, and Moriyasu, 1962; Rainsford and Lloyd Davies, 1965; Van Haaf ten and Sie, 1965; Pag notto and Lieberman, 1967; Docter and Zielhuis, 1967). Most of the publications, however,
TABLE

Metabolite Concentration in Urine after Exposure to Trichloroethylene, Phenol, and Toluene

<table>
<thead>
<tr>
<th>Chemicals exposed at TLV</th>
<th>Urinary metabolites measured</th>
<th>Correction * for urine concentration</th>
<th>Urinary metabolite levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichloroethylene (50 ppm⁴)</td>
<td>Total trichlorocompounds⁴</td>
<td>0.9⁴</td>
<td>421 (291-7-607-7)</td>
</tr>
<tr>
<td></td>
<td>OV (mg/l)</td>
<td>236-7 (167-7-334-6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sp.gr. (mg/l)</td>
<td>265-3 (148-5-473-9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creat. (mg/g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenol (5 ppm⁴)</td>
<td>Total phenols⁴</td>
<td>26.1 (10-1-66-9)</td>
<td>608-9 (358-8-1-003-2)</td>
</tr>
<tr>
<td></td>
<td>OV (mg/l)</td>
<td>23.3 (9-0-60-4)</td>
<td>448-0 (278-6-720-6)</td>
</tr>
<tr>
<td></td>
<td>Sp.gr. (mg/l)</td>
<td>18.9 (7-3-49-0)</td>
<td>394-0 (258-9-599-7)</td>
</tr>
<tr>
<td></td>
<td>Creat. (mg/g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toluene (100 ppm³)</td>
<td>Hippuric acid</td>
<td>0.30 (0-09-0-97)</td>
<td>3.18 (1-79-5-65)</td>
</tr>
<tr>
<td></td>
<td>OV (g/l)</td>
<td>0.29 (0-08-1-05)</td>
<td>2.03 (1-24-3-31)</td>
</tr>
<tr>
<td></td>
<td>Sp.gr. (g/l)</td>
<td>0.23 (0-06-0-88)</td>
<td>2.35 (1-42-3-87)</td>
</tr>
<tr>
<td></td>
<td>Creat. (g/g)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹TLV, 1972, of Japanese Association of Industrial Health; MAK, 1971, of Deutsche Forschungsgemeinschaft
²TLV, 1971, of American Conference of Governmental Industrial Hygienists; MAK, 1971, of Deutsche Forschungsgemeinschaft
³TLV, 1972, of Japanese Association of Industrial Health; the intended value for TLV, 1971, of American Conference of Governmental Industrial Hygienists
⁴Trichloroacetic acid plus trichloroethanol
⁵Free plus conjugated phenols
⁶Sp. gr. = observed value corrected for a specific gravity of urine of 1.016 (Buchwald, 1964)
⁷Creat. = observed value divided by creatinine concentration (Jackson, 1966)
⁸Recalculated from data previously published (Ikeda and Ohtsuji, 1969b)
⁹Upper and lower limits; P = 0-10
¹⁰Minimum and maximum values observed

Dealt with the mean concentration of the metabolites of the compounds under study and less attention was paid to variation in the metabolite concentration at the given atmospheric concentration of the toxic agent. When the screening level is set at the mean of the metabolite concentration corresponding to the TLV, the actual exposure of about half the workers will be underestimated and this is hardly protective of the health of workers. The use of the lower fiducial limit (P = 0.10) as the screening level will result in under-estimation of the exposure intensity at 5%. The degree of risk of error permitted may vary depending on the purpose of the screening test; Ellis (1966), for example, took a 90% confidence limit for the control of lead exposure by means of urinalysis, as in statistical analysis of biological observations in which a 5% or 10% risk is usually taken. It is of practical importance to make clear the percentage risk of misjudgement in establishing the screening level. Repeated and periodic follow-up examinations of the exposed workers combined with a control chart technique (Ellis, 1966) should improve the reliability of the urinalysis as a screening test for excessive exposure.

Thanks are due to Professor M. Nishio (Kyoto University Faculty of Medicine) for his interest in this work, and to M. Ohara for assistance in the preparation of the manuscript.

References


Received for publication November 7, 1972.
Lower fiducial limit of urinary metabolite level as an index of excessive exposure to industrial chemicals
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doi: 10.1136/oem.30.3.289

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