

Biological criteria for selected industrial toxic chemicals: A review

by ROBERT LAUWERYS, M.D., D.Sc.¹

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One of the main objectives of occupational medicine is to prevent the development of occupational diseases. In this respect the biological monitoring of workers exposed to various industrial chemicals may play an important role, either by detecting excessive exposure as early as possible before the occurrence of significant biological changes or by discovering biological disturbances when they are still reversible or have not yet caused any health impairment.

One must recognize that this method of early detection of industrial hazards has not yet reached an advanced stage of development, and the reasons are simple. A rational biological monitoring is only possible when sufficient toxicological information has been gathered on the mechanism of action and/or the metabolism of xenobiotics to which workers may be exposed. For many industrial chemicals relevant information is lacking however. Indeed new industrial chemicals are regularly introduced before any extensive toxicological study has been performed. Furthermore, when basic toxicological investigations (mechanism of action, me-

tabolism) have suggested a potentially useful biological parameter (urinary metabolite, blood enzyme activity, etc.), other prerequisites such as the following must still be met before proposing its use for the routine monitoring of workers exposed to the chemical:

1. If a biological parameter is intended to evaluate the intensity of a biological disturbance (inhibition of plasma pseudocholinesterase, reduction of peak expiratory flow rate, etc.), some knowledge of the health significance of the biological change measured (e.g., correlation with brain true cholinesterase activity) should be available in order to propose a meaningful threshold value for the parameter.

2. If a biological parameter is proposed to evaluate the total uptake (lung, skin, digestive system, etc.) of a foreign chemical or its degree of retention in the organism [body burden = (uptake $\times$ time) — (elimination $\times$ time)], the relationship between these parameters (uptake, body burden) and the rate of variation of the biological parameter must also be known. It should be emphasized that the situation may be very complicated when the metabolic fate of the compound differs according to the route of entry, as has been demonstrated for ethylbenzene (86).

3. When a biological measurement is principally intended to evaluate uptake, the relationship referred to in no. 2 must hold for exposures below the maximum

¹ Unit of Industrial and Medical Toxicology, University of Louvain, Brussels, Belgium.

Reprint requests to: Prof. R. Lauwerys, Unité de Toxicologie Industrielle et Médicale, University of Louvain, 4 Clos Chapelle aux Champs, 12 Brussels, Belgium.

tolerable exposure; hence a biological threshold limit value (TLV) can be proposed.

4. For evident practical reasons a selected parameter should be sufficiently stable to allow storage of the biological samples for a certain period of time and it should be amenable to a nontime-consuming analysis by a not too sophisticated technique.

5. The precision and the accuracy of the analysis should be satisfactory. Several intercomparison programs for the analysis of industrial chemicals in biological material have indeed stressed the analytical difficulties associated with these measurements (28, 29, 40, 82, 159, 162, 170, 192).

For many currently used industrial chemicals one or all of the preceding prerequisites are lacking, which of course limits the possibilities of specific biological monitoring.

When such specific (or at least oriented) biological measurements are feasible, the approach offers important advantages over monitoring the air of the work place. The two main advantages are (a) that it takes into consideration absorption by all the routes, not only through the lungs, and (b) that it may consider individual differences in the susceptibility to the chemical or differences in its rate of absorption, distribution, biotransformation, and excretion. Each worker is thus his own integrator of the total exposure (181).

The purpose of this review is to discuss some industrial toxicological hazards for which, on the basis of current scientific knowledge, a biochemical parameter may be useful in either detecting functional perturbations at an early stage or evaluating the intensity of exposure. This paper does not deal with the physiological parameters (like lung function tests) in cases of exposure to lung irritants, but is limited to the chemical analyses which can be performed on biological material. However, although in many circumstances a biological parameter can be proposed, no meaningful biological TLV can yet be defined because clinical studies (on workers or on volunteers) are lacking or inadequate.

Before specific compounds are dealt with, some general remarks are relevant. When biological monitoring consists of sampling and analyzing urine, it is usually performed on "spot" specimens because routine collection of 24-h samples from workers is impractical (94). It is therefore advisable to correct the results for the dilution of the urine. Two methods of correction have been used: (a) expression of the results per gram of creatinine or (b) adjustment to a constant specific gravity. Although there is no general superiority for creatinine adjustment over specific gravity, creatinine correction is better for very concentrated and very dilute samples (94). Furthermore, in the case of glucosuria and probably proteinuria, the specific gravity adjustment may give results that are too erroneous. In our laboratory my coworkers and I also use creatinine adjustment. (The average daily excretion of creatinine in adults is 1.7 g.) Whatever the method of correction it should be stressed that analyses performed on too diluted a urine specimen (specific gravity less than 1.010) are not reliable. In some circumstances it may be feasible to report results in excretion rates (i.e., quantity/time unit), which supposes the collection of urine during a well-defined period of time (one or a few hours). One must however recognize that this method, which is certainly more accurate than spot sample analysis, is usually too elaborate for the routine control of workers.

When the large interindividual variability and/or the high "background" level of the biological parameter selected makes the interpretation of a single measurement difficult, it is sometimes useful to analyze biological material collected before and after the exposure period. The change in the biological parameter due specifically to exposure can then be better assessed.

I. BIOLOGICAL TESTS FOR ORGANIC SUBSTANCES

The majority of volatile organic substances absorbed by inhalation or through the skin are partially eliminated unchanged with the expired air and partially metab-

olized into more polar derivatives, which are excreted in the urine.

Usually the metabolism of organic substances *in vivo* is rapid, and the excretion of the compound and/or its metabolites is, with a few exceptions, complete within 2 or 3 days. Therefore, when a biological method is used for monitoring exposure to these substances, the biological medium to be analyzed (blood, urine, expired air) must be collected at well-defined time intervals after the beginning of exposure, usually at the end of a work shift or, as indicated earlier, before and after the work period.

Two approaches have usually been followed in evaluating exposure to volatile organic substances: (a) determination of the main metabolite in urine (which requires a knowledge of the biotransformation undergone by the chemical *in vivo*) and (b), more recently, measurement of the parent compound in the expired air.

AROMATIC HYDROCARBONS

Benzene

Benzene is one of the most, if not the most, toxic aromatic hydrocarbons. Its metabolism has been the object of detailed studies (133, 248, 249, 263, 281, 282, 362).

A fraction of the absorbed benzene is excreted unchanged mainly in the expired air, partly in the urine. The remaining fraction is metabolized probably by the liver microsomal enzymes (fig. 1).

The first reaction catalyzed by these enzymes is the transformation into benzene epoxide, a very reactive intermediate that either binds directly to cellular constituents (DNA, proteins, etc.), and is suspected for being responsible for the myelotoxic action of benzene, or is further transformed into other benzene derivatives. Benzene epoxide may be transformed non-enzymatically into phenol, which is then

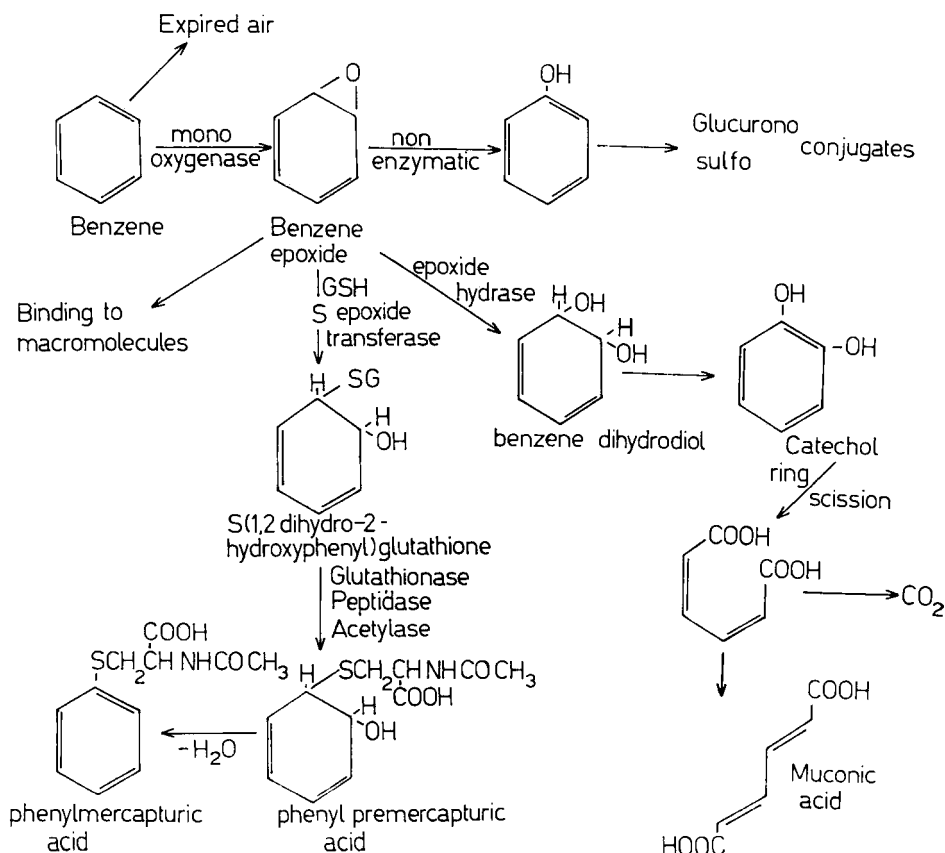


Fig. 1. Metabolic biotransformations undergone by benzene *in vivo*.

conjugated with glucuronic acid or sulphate. The glucurono and sulfoconjugates of phenol are then excreted in the urine. The epoxide may also react with glutathione to yield S (1,2 dihydro-2-hydroxyphenyl) glutathione. The subsequent action of a glutathionase in the presence of a glutamine acceptor, a peptidase and acetyl CoA acetyltransferase, gives rise to a premercapturic acid, i.e., S (1,2 dihydro-2-hydroxyphenyl) acetyl-L-cysteine) premercapturic acid, which is excreted as such in the urine. When urine is treated with mineral acids, the premercapturic acid is transformed into mercapturic acid. Under the action of the enzyme epoxide hydrazase, trans 1,2 dihydro, 1,2 dihydroxybenzene is formed and is quickly transformed into catechol. This metabolite has also been considered responsible for the bone marrow lesions induced by benzene (176). After a ring scission reaction catechol is transformed into trans-trans muconic acid, excreted in the urine, and carbon dioxide, excreted with the expired air.

Phenol and its conjugates, phenylsulfate and phenylglucuronide, are the major metabolites of benzene (79, 299, 362).

The knowledge of the fate of benzene *in vivo* has given rise to several biological exposure tests: (a) the ratio between inorganic and organic sulfates in urine, (b) concentration of total (free and conjugated) phenol in urine, (c) benzene determination in blood and in expired air (185).

The ratio between inorganic and organic sulfates in urine is normally more than 85 %. Exposure to benzene produces a decrease in this ratio since some metabolites of benzene are eliminated as sulfoconjugates. The decrease is roughly proportional to the degree of exposure (91, 328). In subjects who are free of any hepatic disease and who exhibit a normal sulfoconjugation capability the finding of a ratio below 70 % indicates an exposure above 40 ppm; a ratio below 40 % results from an exposure to more than 75 ppm. The sensitivity and the specificity of this test are thus very limited since an exposure on the order of 10 ppm [time-weighted average recommended in 1974 by the National Institute for Occupational Safety and Health (NIOSH), U.S.A. (228)] would cause only a slight, and probably not sig-

nificant, reduction in the ratio, and numerous hydroxylated organic chemicals are also excreted in urine as sulfoconjugates.

Contrary to substituted benzene derivatives (toluene, xylene, etc.) benzene gives rise to phenol *in vivo*, and therefore the measurement of urinary phenol excretion has been proposed as an exposure index. The sensitivity of this analysis is sufficient since workers not exposed to benzene or phenol excrete less than 20 mg of phenol per gram of creatinine, on the average 5 mg per gram of creatinine (SD = 2.7 mg/g creatinine) [measurement performed with a specific gas chromatographic technique (41)]. After an 8-h exposure to an average benzene concentration of 10 ppm, the phenol concentration in urine collected at the end of a working shift would be, as a group average, around 70 mg per liter (79, 328). The large difference between normal phenol concentrations in urine and those found when the time-weighted average exposure reaches 10 ppm allows therefore an early detection of benzene exposure. It is true that there are interindividual variations in phenol excretion and that an isolated result has limited value in evaluating the hygienic conditions of the work place. More useful in this regard is the information drawn from the urine analysis of a group of workers or from the evolution of the phenol excretion on follow-up urine samples obtained at the beginning and at the end of the work day.

It should also be kept in mind that all the methods for urinary phenol analysis do not have the same specificity. The interpretation of the results must take care of this factor. In general the various colorimetric techniques (46, 245, 264, 328, 356) lack specificity because some urinary cresols react also like phenol. It is therefore preferable to use a gas chromatographic method more specific and precise than the colorimetric methods (41, 195, 343).

It should also be kept in mind that dermal application of phenol-containing preparations, exposure to phenol itself, and some gastrointestinal disorders favoring the bacterial degradation of tyrosine and phenylalanine (84) increase urinary phenol concentration.

The determination of benzene itself in

blood and in expired air has also been proposed for the evaluation of the degree of exposure (7, 233, 293, 325, 367). The lack of valuable information on the relationship between atmospheric and blood concentrations of benzene prevents the recommendation of a biological TLV for benzene in blood. Benzene concentrations in expired air after the end of exposure follow a more or less exponential decline (234). In fact one deals with several exponential curves which overlap each other and represent the clearance of the solvent from various body compartments. With a well-standardized protocol it is possible to demonstrate the existence of a satisfactory relationship between environmental exposure levels and benzene concentrations in exhaled breath (293, 306). However sufficient data, with which to define the conditions of breath analysis during routine monitoring (e.g., time of sampling) and the biological TLV for exhaled air, are still lacking.

Toluene and xylene

The metabolism of toluene and xylene is rather similar. In contrast to benzene these substances are not significantly transformed in phenol derivatives (185, 227).

The fraction of toluene which is not eliminated unchanged in the expired air is oxidized by transformation of the methyl radical into a carboxyl radical (by the microsomal monooxygenase system), which is then conjugated with glycine to produce hippuric acid (fig. 2). The meta and para isomers of xylene are, like toluene, principally oxidized into toluic acids, which are then conjugated with glycine to produce meta and para methylhippuric acids. The ortho isomer, which is less frequently used, is also partially hydroxylated. The

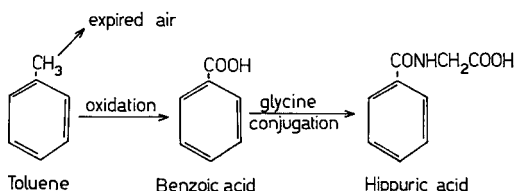


Fig. 2. Metabolic biotransformations undergone by toluene in vivo.

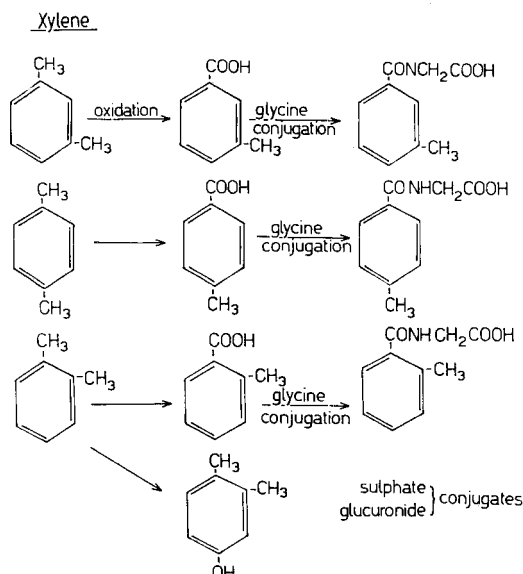


Fig. 3. Metabolic biotransformations undergone by xylene in vivo.

resulting xylenol is then conjugated with sulphate or with glucuronic acid. (fig. 3).

Several studies have demonstrated that there exists a significant correlation between the intensity of exposure to toluene and xylene and the amount of hippuric and methylhippuric acid excreted in the urine (146, 238, 246).

As is the case for benzene, it must be pointed out that all the analytical procedures do not have the same specificity, a fact which may explain the variability of "normal" values of hippuric acid found by different laboratories.

My colleague and I have recently developed a specific gas chromatographic technique for measuring hippuric and methylhippuric acid in urine (42) and have found that, although large variations in urinary hippuric acid excretion exist between non-occupationally exposed individuals (benzoic acid is a constituent of many food items), its excretion rarely exceeds 1.6 g/l (on the average 0.8 g/g creatinine). Methylhippuric acid is not normally found in urine. This result agrees with those reported by other authors (48, 145).

According to Pagnotto and Lieberman (246), who measured hippuric acid by a nonspecific spectrophotometric technique, an exposure to 100 ppm toluene [current atmospheric TLV proposed by the Ameri-

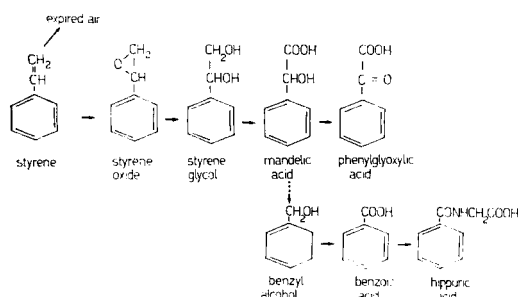


Fig. 4. Metabolic biotransformations undergone by styrene in vivo.

can Conference of Governmental Industrial Hygienists (ACGIH) in 1974 and by NIOSH in 1973 (227)] would produce a urinary hippuric acid content of about 4 g per liter in samples collected at the end of the work shift. Ogata et al. (238) who used a more elaborate and specific colorimetric technique (237), proposed slightly lower values. With their method an exposure to 100 ppm of toluene would produce an average hippuric acid concentration of 2.8 g per liter (corrected for a specific gravity of 1.024) in urine collected in the second part of a 7-h exposure period. Their finding agrees with data reported by Ikeda and Ohtsuji (146).

Under the same conditions (7-h exposure to 100 ppm) urinary methylhippuric acid concentration is on the order of 2.5 g per liter (238).

The value of the expired air and blood determinations of toluene in evaluating the degree of exposure has also been tested. According to Åstrand et al. (11) the best approach is to measure the content of solvent in alveolar air samples collected during exposure. At rest, the mean value for alveolar air concentration found during exposure to 100 ppm of toluene is 18 ppm. In steady-state atmospheric toluene concentrations, alveolar air concentration increases as the atmospheric concentration increases. Determination of the toluene concentration in a venous blood sample has a very limited value in providing a correct view of the amount of toluene accumulated in the tissues. Furthermore the results of Åstrand et al. (11) suggest that: "neither alveolar air samples nor venous blood samples taken at given intervals after the conclusion of a period of exposure can provide sufficiently accu-

rate information on the average amount of solvent in inspired air at a working place or on the magnitude of an individual's uptake."

Nomiyama and Nomiyama (233, 234) found also that after the cessation of exposure women eliminated less toluene with the expired air than men.

Mesitylene-1,3,5 -trimethylbenzene

Mesitylene is a solvent which is oxidized in the organism to give 3,5 dimethylbenzoic acid or mesitylenic acid (177), which is then conjugated with glycine. This metabolite can be recovered in the urine of workers exposed to mesitylene, but no data have yet been published which suggest a possible biological TLV.

Styrene or vinylbenzene

Styrene is extensively used in the manufacture of plastics. It enters the organism mainly through the lungs and the skin. Its metabolism has been thoroughly studied in man and can be summarized in the following manner (fig. 4). As for any volatile compound, a fraction of the dose absorbed (mostly via the lungs and the skin) is excreted unchanged with the expired air. What remains is oxidized into styrene oxide, which is hydrolyzed into styrene glycol. This metabolite is then oxidized into mandelic acid. In man mandelic acid is either excreted as such in urine or further oxidized into phenylglyoxylic acid, which is also excreted by the kidneys (18, 241). When exposure is important (e.g., atmospheric concentration exceeding 100 ppm), the in vivo concentration of mandelic acid is sufficient to significantly stimulate another pathway, i.e., the decarboxylation of mandelic acid into benzyl alcohol, the precursor of hippuric acid (150).

Man however seems to have a relatively poor ability to convert mandelic acid to benzyl alcohol. Therefore in workers moderately exposed to styrene (< 100 ppm) only an increased urinary excretion of mandelic and phenylglyoxylic acid is usually found.

After styrene exposure the urinary pattern of excretion of the two main metabolites is different. The biological

half-life of phenylglyoxylic acid in urine is greater than that of mandelic acid (150, 259), and it is a function of the intensity of exposure (259).

According to Härkönen et al. (132) workers exposed for 8 h to 200 ppm of styrene excrete about 2 g of mandelic acid per liter of urine. Bardodej and Bardodejova (17, 18) have reported values 50 % greater (3 g/l) for the same exposure. According to Götell et al. (121) 1 g of mandelic acid per liter of urine would indicate a time-weighted exposure of 50 ppm.

My coworkers and I have found that, when the phenylglyoxylic acid concentration in urine collected at the end of the working period does not exceed 350 mg/g creatinine, an exposure above the TLV proposed by the ACGIH in 1974 (100 ppm) is unlikely (259). It may also be interesting to control that the urine is emitted during an exposure period by measuring the ratio mandelic acid/phenylglyoxylic acid, which should then exceed a value of 2 (259). Götell et al. (121) reported that, when styrene exposure exceeds 150 ppm, the urinary levels of phenylglyoxylic and mandelic acids are no longer proportional to the solvent concentration in air.

Gas chromatographic and colorimetric techniques are available for measuring the two main metabolites in urine (44, 96, 241).

Since there exists a significant correlation between the concentration of styrene in the alveolar air during exposure and the environmental concentration (243), the magnitude of the latter can also be evaluated by sampling the alveolar air at the work place [10 to 25 ppm styrene in the alveolar air for an exposure of 100 ppm (243, 307)]. Such a measurement, which must be performed at the site of exposure, has of course a limited interest. It does not integrate the total exposure during a time interval. It is simply an instantaneous measurement reflecting the intensity of exposure at the time of sampling. Stewart et al. (307) have indicated that, as for several halogenated solvents, there also exists a good correlation between the pulmonary clearance of styrene after the end of exposure and the intensity of the latter.

Three types of information would therefore be required to evaluate the average

exposure concentration: (a) the expired air concentration, (b) the time interval between sampling and the end of exposure, and (c) the duration of the latter. According to Oltramare et al. (243) individual differences partly due to differences in body fat content, minute-ventilation, and cardiac output limit the interest of such an approach.

HALOGENATED HYDROCARBONS

Trichloroethylene

The amount of absorbed trichloroethylene that is not excreted unchanged with the exhaled breath is metabolized into chloral hydrate, which is then transformed into trichloroacetic acid and trichloroethanol. Both metabolites are excreted by the kidney (filtration and tubular secretion) (113). Trichloroethanol is partly conjugated with glucuronic acid (200) (fig. 5).

Several studies have investigated the interest of determining both metabolites in urine in order to evaluate environmental exposure to trichloroethylene (231, 255, 326). The biological half-lives of trichloroethanol and trichloroacetic acid are different; that of the latter is greater than that of the former because of the binding of the trichloroacetic acid to plasma proteins (97, 147, 163, 164, 222, 239). Müller et al. (222) evaluated the biological half-life of trichloroethanol at 12 h and that of trichloroacetic acid at 100 h in volunteers exposed to 50 ppm of trichloroethylene (6 h a day for 5 days). Thus the trichloroethanol concentration in urine

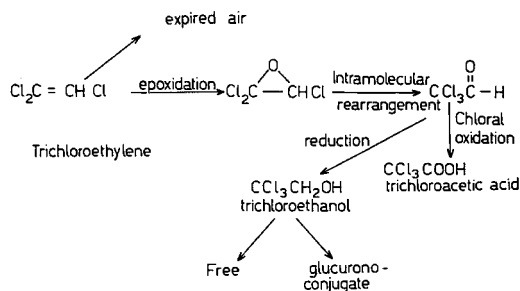


Fig. 5. Metabolic biotransformations undergone by trichloroethylene in vivo.

reflects the environmental exposure of the same day even though that of trichloroacetic acid is still influenced by exposure from preceding days. Frant and Westendorp (107) calculated that exposure for several days to 100 ppm trichloroethylene is associated with a urinary excretion of 200 mg of trichloroacetic acid per liter. On the other hand Grandjean et al. (124) stated that the ratio of trichloroethylene in air (in ppm) over trichloroacetic acid in urine (in mg/l) is 3 : 1, which means that after exposure to 100 ppm of trichloroethylene the urinary concentration of trichloroacetic acid would be approximately 30 mg/l. Recently the subcommittee of the Hygiene Standards Committee of the British Occupational Hygiene Society (317) endorsed a recommendation that a level of 100 mg/l of trichloroacetic acid in urine (after the application of a correction to a specific gravity of 1.016) corresponded to 100 ppm trichloroethylene in air, but details of the study on which this recommendation is based have not yet been published.

Several Japanese workers (231, 239, 326) have recommended measuring both metabolites (total trichloro compounds) to estimate trichloroethylene exposure. Indeed animal experiments recently confirmed by human observations (97, 148, 164) have demonstrated that, when the atmospheric concentration of trichloroethylene exceeds 50–100 ppm, a greater fraction of trichloroethylene is transformed into trichloroethanol rather than into trichloroacetic acid.

Nomiyama and Nomiyama (232) also found a sex difference in trichloroethylene metabolism. Within 24 h after the end of exposure urinary excretion of trichloroacetic acid was greater in women than in men; the opposite was true for trichloroethanol. This observation was confirmed by Kimmerle and Eben (164).

Nomiyama (231) proposed a regression equation permitting the calculation of the average air concentration of trichloroethylene on the basis of the concentration of total trichloro compounds in urine collected at different time intervals (up to 10 days) after the end of exposure.

Roughly one can say that a time-weighted average exposure of 100 ppm of trichloroethylene (current ACGIH and

NIOSH TLV) is associated with an excretion of 500–600 mg of total trichloro compounds per gram of urine creatinine (urine collected at the end of the work period) (231). However, because of the prevalence of subjective complaints and psychological disturbances (148, 279) when the atmospheric concentration exceeds 50 ppm, reduction of the TLV to this level seems justified. This level would correspond to a biological TLV of approximately 250 mg per gram of creatinine for total trichloro compounds (148, 222, 231). It should be stressed that, as for any urinary metabolite, this relationship is only valid on a group basis because large individual differences exist in the rate of excretion of trichloroethanol and trichloroacetic acid.

Very sensitive and precise gas chromatographic techniques are now available for measuring both metabolites (43, 240).

Müller et al. (222) proposed determining trichloroacetic acid in plasma and trichloroethanol in whole blood rather than in urine. After the exposure of volunteers to 50 ppm trichloroethylene for 5 days (6 h a day) trichloroacetic acid in plasma reaches a level of 50 μg per ml and that of trichloroethanol in whole blood, 2.3 $\mu\text{g}/\text{ml}$.

Stewart and his collaborators (309, 313) extensively studied the pulmonary clearance of several aliphatic halogenated hydrocarbons and advocated this method of biological monitoring. According to this group of workers trichloroethylene concentration in expired alveolar air collected during exposure reflects the current atmospheric concentration (like for styrene), whereas that in alveolar air 16 h after the end of exposure (i.e., at the start of the next exposure period) correlates with the average airborne exposure.

Thus as a screening monitoring system Stewart et al. (313) have recommended the analysis of expired air before resuming work. Sixteen hours after an 8-h exposure to 100 ppm of trichloroethylene (integrated exposure of 800 ppm) its concentration in alveolar air would not exceed 1 ppm. Such an approach — evaluation of the individual uptake of trichloroethylene by expired air analysis at the beginning of the next period of exposure — has also been recommended by Pfäffli and Backman (258).

Other halogenated hydrocarbons

The capacity of humans to metabolize tetrachloroethylene (148, 239) and 1,1,1 trichloroethane (methylchloroform) (305) is limited.

After repeated exposure to increasing concentrations of tetrachloroethylene the urinary excretion of total trichlorocompounds levels off rapidly at about 50 mg per gram of creatinine when the airborne tetrachloroethylene concentration reaches 50 ppm (148).

Stewart and Rowe (305) also found that in humans exposed to 500 ppm methylchloroform (7 h a day for 5 days) the amount of total trichloro-derivatives found in urine never exceeded one-tenth of the amount found after exposure to 200 ppm trichloroethylene. This observation was recently confirmed by Seki et al. (287). They estimated that exposure to 50 ppm of trichloromethylene and methylchloroform gives rise to a urinary excretion of 368 and 14 mg of total trichlorocompounds per liter of urine, respectively.

Comparing the urinary excretion of trichloroacetic acid and trichloroethanol in rats and mice exposed for 8 h to 200 ppm of various halogenated aliphatic hydrocarbons (1,1,1 trichloroethane; 1,1,2-trichloroethane; 1,1,1,2 — tetrachloroethane; 1,1,2,2 tetrachloroethane, trichloroethylene and tetrachloroethylene), Ikeda and Ohtsuji (149) found that all compounds except 1,1,2-trichloroethane yielded an increased urinary excretion of both metabolites. This phenomenon was the most important for 1,1,1,2 tetrachloroethane (149, 371) and trichloroethylene and much less important for tetrachloroethylene. In view of the infrequent use of 1,1,1,2 tetrachloroethane one can consider that the determination of total trichlorocompounds in urine has mainly a practical value for the evaluation of trichloroethylene exposure.

Although total trichlorocompounds in urine increase only slightly following exposure to methylchloroform, Seki et al. (287) believe that their determination could nevertheless be useful to evaluate exposure to this solvent. As indicated earlier, an exposure to 50 ppm of methylchloroform would result in a urinary excretion of 15 mg of total trichlorocompounds per gram of creatinine. However

their data do not permit extrapolation to exposure around the current ACGIH TLV (250 ppm).

According to Grigorescu and Tora (cited by Boudene 1970) (36) the principal urinary metabolite of vinyl chloride is monochloroacetic acid, the concentration of which is related to the degree of exposure. No recent information is available on this subject, which deserves further research.

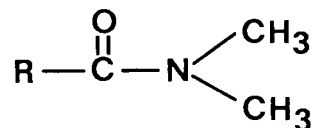
As in the case of trichloroethylene the determination of respiratory concentration has also been proposed for estimating environmental exposure to several aliphatic halogenated hydrocarbons (carbon tetrachloride, tetrachloroethylene, methylchloroform, vinyl chloride, dichloromethane) (19, 76, 268, 302, 303, 304, 308, 310).

Some of these chemicals are also detectable in circulating blood (76) where their concentration should probably correlate with that in expired air. The data available are however insufficient for proposing meaningful biochemical TLVs for blood or expired air.

It is relevant to note here that an increased blood carboxyhemoglobin concentration has been observed in workers exposed to dichloromethane (methylene chloride) (311, 312). The carboxyhemoglobin level can reach 10 to 15 % following 1 h of exposure to 1,000 ppm dichloromethane.

DIMETHYLAMIDES

Dimethylamides have the following general structure:



N methylformamide and N methylacetamide are the main metabolites resulting from the demethylation of the corresponding dimethylamide in vivo. They are excreted in the urine (20, 21, 165, 166). Preliminary results from a survey of workers exposed to dimethylformamide during the production of acrylic resin suggest that the determination of N methylformamide in urine could be useful in evaluating the degree of exposure (Lauwerys et al., unpublished results). On the

basis of studies on human volunteers Kimmerle and Eben (166) concluded that a concentration of N-methylformamide above 50 mg per 24-h urine indicates exposures exceeding 20 ppm.

ALCOHOLS, GLYCOLS, PHENOL AND DERIVATIVES (see also pesticides)

Methanol can be determined in blood and in urine. Published cases of acute methanol poisoning, usually resulting from the absorption of adulterated liquor or methanol antifreeze, have indicated that there is some relationship between the severity of intoxication and the blood methanol concentration.

Human experiments have also shown that the methanol concentration in urine collected at the end of an exposure period seems to correlate with time and exposure levels (194). On the basis of these experiments in man and the observations made by Elkins (cited by Tréon) (336) in industry, one can roughly estimate that in the urine of workers exposed to 200 ppm of methanol (current ACGIH TLV) one should find less than 5 mg of methanol per liter of urine.

Oxalic acid is one of the metabolites of ethylene glycol (110, 213) and methylcellosolve (monomethyl ether of ethylene glycol) (230) which is excreted by the kidneys. The limited data available do not permit a proposal of a biological standard for this metabolite.

Almost 100 % of the phenol absorbed through the lung and the skin is excreted in the urine within one day, mostly in a conjugated form (242, 262). Piotrowski (262) estimated that in workers exposed for 8 h to 1.3 ppm (5 mg/m³) or 5 ppm (19 mg/m³) of phenol (current Soviet and ACGIH TLV) the excretion rate at the end of the exposure period would reach about 4.4 and 15.3 mg per hour, respectively. This estimation agrees well with the observations of Ohtsuji and Ikeda (242). According to their regression line one should find approximately 300 mg of phenol per gram of creatinine in urine samples collected toward the end of an 8-h exposure to 15 mg phenol/m³. The same authors found that neither urinary ethereal sulphate nor urinary ethereal glucuronide was a good index of phenol exposure.

AMINO AND NITRO COMPOUNDS (see also pesticides)

Several aromatic amino and nitro compounds are methemoglobin producing agents, and exposure to these agents should be kept below the level producing change in the blood methemoglobin level. In normal subjects who were not occupationally exposed to methemoglobin producing substances and who had abstained from smoking for at least 12 h previously, Gobbi et al. (117) found a mean methemoglobin level of 1.16 % (SD = 0.81 %).

For aniline and nitrobenzene the determination of the main urinary metabolites — p-aminophenol and p-nitrophenol, respectively — is certainly a more sensitive method of monitoring than methemoglobin determination. After 6 h of exposure to an airborne vapor concentration of 1 ppm of nitrobenzene (current ACGIH TLV) the urinary concentration of p-nitrophenol reaches approximately 5 mg/l (261). A dangerous exposure to aniline is suspected when the p-aminophenol concentration exceeds 50 mg/l (215). A reasonable biological TLV should probably be on the order of 10 mg/l.

PESTICIDES

Organophosphorus and carbamate insecticides

The depression of plasma and/or erythrocyte cholinesterase is usually regarded as a good indice of the absorption of cholinesterase inhibiting pesticides (organophosphorus esters, N methyl or N dimethylcarbamate esters).

The various techniques available for measuring these enzymes have been reviewed elsewhere (13, 361, 368).

Some pitfalls should be recognized. Inhibition of the enzymes by free active pesticides may occur during blood storage, and in that case cholinesterase activity is not a reflection of the true activity *in vivo* (342). On the other hand carbamylated cholinesterases and also some phosphorylated cholinesterases can be significantly reactivated during storage. The two kinds of error, further inhibition or partial recovery after sampling, must be

considered when selecting the conditions of assay (technique, duration of storage, etc.). The selection of the enzyme activity to be determined (red blood cell or plasma) depends on the relative affinity of the pesticide for both enzymes. Usually, but there are several exceptions, plasma cholinesterase is more sensitive to inhibition by organophosphate and carbamate insecticides than the erythrocyte enzyme. Since there is a great interindividual variability in blood cholinesterase activity, it is certainly more meaningful to compare exposure values with preexposure levels. A 50 % reduction in activity requires removal of the worker from exposure.

Although cholinesterase enzyme determinations are sufficiently sensitive and specific for monitoring programs (mostly if preexposure activities are known), they sometimes raise difficult problems for adequate sample conservation before analysis. Therefore in some circumstances it may be interesting to consider whether the search for a urinary metabolite may not be more practical.

Various dialkylphosphates which are hydrolytic metabolites of many organophosphorus esters can be measured in urine by gas chromatography (292). Skafik et al. (292) proposed such a measurement for human monitoring programs, but a biological threshold should then be established for each pesticide. Indeed it is clear that the amount of dimethylphosphate tolerable in urine should depend on whether the worker has been exposed to methylparathion or fenitrothion, both of which are dimethylphosphate esters but have a different degree of toxicity.

The determination of urinary 4-nitrophenol excretion has been demonstrated to be a reliable index of parathion [0,0-diethyl 0 (4-nitrophenyl) phosphorothioate] parathion methyl and EPN [0-ethyl 0-(4-nitrophenyl) phenylphosphonothioate] exposure (9, 95, 111, 223, 270, 369), even more sensitive as an absorption index than blood cholinesterases. This metabolite can be readily measured by a colorimetric or a gas chromatographic procedure (38, 62, 95, 354). A biological threshold of 100 $\mu\text{g/l}$ in urine has been proposed (215). This value has probably a very high margin of safety since excretion rates of more than

100 $\mu\text{g/h}$ have been found in sprayers exposed to parathion without symptoms of intoxication (369).

Hayes (134) concluded from the work of Arterberry et al. (9) that the absorption of parathion is tolerated without illness and with little or no reduction in cholinesterase activity as long as the concentration of p-nitrophenol in urine does not rise much above 2 mg/l. Cases of poisoning have however been reported by Arterberry et al. (9) in which the p-nitrophenol excretion was lower than 2 mg/l (0.9, 0.57 and 1.6 mg/l).

Results obtained by Roan et al. (270) indicate that the determination of ethyl- or methylparathion in serum samples via gas chromatography is even more sensitive than the urine p-nitrophenol measurement. For many other anticholinesterase pesticides [Abate or 0,0,0',0' tetramethyl 0,0' thiodi-p-phenylene phosphorothioate; fenitrothion or 0,0-dimethyl 0-(3-methyl-4-nitrophenyl) phosphorothioate; dicapthion or 0 (2-chloro-4-nitrophenyl) 0,0-dimethyl phosphorothioate; fenchlorphos or 0,0-dimethyl 0-(2,4,5-trichlorophenyl) phosphorothioate; dursban or 0,0 diethyl 0-(3,5,6-trichloro-2-pyridyl) phosphorothioate; carbaryl or 1-naphthyl methylcarbamate; 2 isopropoxyphenyl methylcarbamate, etc.] the main urinary metabolites in humans are known or suspected from animal experiments (thiodiphenol; p-nitrocresol; 2-chloro-4-nitrophenol; 2,4,5 trichlorophenol; 3,5,6-trichloro-2-pyridinol, 1-naphthol; 2-isopropoxyphenol) and are amenable to analysis by unsophisticated techniques (33, 70, 291). The measurement of these metabolites may therefore constitute the basis of a biochemical test of exposure. However, insufficient human data exist for the proposal of meaningful biological TLVs for the majority of these metabolites, and therefore more epidemiologic studies are required among workers exposed to these pesticides.

As Hayes (134) pointed out, both approaches, measurement of cholinesterase activity and pesticide metabolite determination in urine, give complementary information because metabolite excretion occurs rather rapidly while enzyme activity recovers slowly. Thus cholinesterase determination integrates the effects of exposure during a long time interval (several

weeks) while metabolite measurement gives information on very recent exposure.

Other pesticides

Organochlorine pesticides can be determined in blood usually by gas chromatography (64, 65, 224, 247, 314). Their plasma concentrations are a satisfactory index of total body burden. This has been well demonstrated in man or in laboratory animals for pp'DDT, lindane, dieldrin, endrin, and telodrin (66, 90, 143, 152, 173, 216, 224, 271, 370). According to Jager (152) the threshold level in the blood below which no signs or symptoms of intoxication occur is at 0.20 $\mu\text{g/ml}$ for dieldrin and 0.015 $\mu\text{g/ml}$ for telodrin. Brown et al. (39) put the threshold level for dieldrin in the blood at 0.15 $\mu\text{g/ml}$. Data obtained by Kolmodin-Hedman (173) suggest that exposure to lindane induces drug oxidation in man at plasma levels above 0.010 $\mu\text{g/ml}$ and higher and that a plasma level of total DDT under 0.2 $\mu\text{g/ml}$ would not modify drug metabolism. Determination of the serum lipoprotein pattern of workers exposed to lindane (detection of hyperalpha-lipoproteins) has also been recommended (173).

According to several authors (85, 193, 369), the urinary excretion of dichlorodiphenylacetic acid (DDA) could be used as an indicator of exposure to DDT. Both colorimetric and gas chromatographic methods are suitable for its determination (193).

Some phenol derivatives used as herbicides (2 methyl-4,5-dinitrophenol or DNOC; 2 sec butyl 4,6-dinitrophenol or DNBP) undergo various metabolic transformations, among them nitroreduction. The determination of corresponding aminoderivatives in urine could constitute the basis of a biochemical test of exposure.

The fungicide pentachlorophenol, which is a strongly acidic phenol, is mostly excreted unchanged in human urine. A urinary concentration of pentachlorophenol below 10 mg per liter seems tolerable. This compound can be measured by gas chromatography with flame ionization or with an electron-capture detector (63, 269). Tetrachlorohydroquinone can also be found in the urine of workers occupationally exposed to pentachlorophenol (3).

II. BIOLOGICAL TESTS FOR INORGANIC AND ORGANO-METALLIC SUBSTANCES

ARSENIC

Exposure to arsenic or its derivatives results in an increased urinary excretion of arsenic (260, 357). Initially Elkins (92) proposed a toleration of a urinary excretion below 1 mg per liter, which corresponds to a TLV of 0.25 mg/m^3 for As_2O_3 .

However, since arsenic is now recognized as a human carcinogen, the NIOSH (226) has recommended that arsenic and/or its derivatives should not be detectable in workroom air. Therefore no increase of urinary arsenic above the "background" level ($< 100 \mu\text{g/l}$) is acceptable (92, 118).

Arsenic determination in hair is considered unreliable for monitoring workers' exposure because it is difficult to distinguish between externally deposited arsenic and that systemically incorporated in the hair (357).

BERYLLIUM

Although the appearance of beryllium in urine may be useful to confirm current or previous exposure to this chemical, no firm relationship between the intensity of exposure and urinary excretion has been established (74, 87, 172). Indeed it is even possible to find no beryllium in the urine of workers with pulmonary granulomatosis (172).

CADMIUM

Persons not occupationally exposed to cadmium usually excrete less than 4 μg of cadmium per gram of creatinine in urine (188, 196, 274, 348).

Exposure to cadmium results in an increased urinary excretion of the metal (189, 199). It is still debatable however whether the cadmium concentration in urine reflects cadmium uptake. Indeed it is well known that the development of tubulopathy following cadmium exposure is associated with a rise in cadmium excretion even if exposure does not increase (1, 158, 189, 274). Nevertheless, if one does

not take into consideration persons already suffering from cadmium nephropathy and already excreting large amounts of proteins, there is a significant relationship between cadmium exposure and the cadmium concentration in urine (189, 210).

Since the TLV for cadmium (dust and fumes) in air is the object of debate and varies from one country to the other between 200 μg and 10 $\mu\text{g}/\text{m}^3$, it may be unwise to propose a biological TLV for cadmium in urine. It has been observed however that kidney lesion is absent when workers excrete less than 15 μg per gram of creatinine (189, 210).

The measurement of specific proteins (lysozyme, ribonuclease, β_2 -microglobulin, albumin) in urine or the determination of their renal clearances may be useful for the early detection of renal involvement following cadmium exposure (109, 274), but it should be stressed that such changes, when present, reflect a tissue injury which may be irreversible and should therefore not be tolerated.

CARBON DISULFIDE

Approximately 70 % of the carbon disulfide retained in the organism is metabolized and excreted in urine as organic sulfates or other sulfur compounds like thiourea, thiocarbamide and 5-mercaptothiazolidone (253, 254, 329).

These metabolites are probably responsible for the iodine azide reaction ($2 \text{NaN}_3 + \text{I}_2 \longrightarrow 3 \text{N}_2 + \text{NaI}$) catalyzed by the urine of exposed workers. This reaction has been proposed for the control of workers exposed to carbon disulfide (77, 347). It should be stressed that this analysis is not specific for carbon disulfide since other substances like dithiocarbamate fungicides (Thiram, Ziram, Zineb, etc.), antabuse, and mercaptobenzoimidazole, which yield an increased excretion of bivalent sulfur, influence the reaction (106, 250).

According to the method developed by Djurić et al. (77) the exposure coefficient calculated from urine voided at the end of a work shift should be above 6.5 when exposure does not exceed 20 ppm.

The same group of workers have recently proposed a test to detect those

workers who could be hypersusceptible to the effects of carbon disulfide (78). After the oral administration of 0.5 g of disulfiram the amount of diethyldithiocarbamates (DDC) present in urine collected 5 h after administration was determined. Since they found that the DDC excretion was the lowest in a group of intoxicated workers, they speculated that the disulfiram test could be a useful tool in predicting the susceptibility of each individual to carbon disulfide.

CARBON MONOXIDE

Under stable conditions (pO_2 , lung ventilation, etc.) there is an excellent correlation between the intensity and duration of exposure to carbon monoxide and the amount of carboxyhemoglobin in blood. The concentration of carbon monoxide in expired air is also a reflection of the amount of circulating carbon monoxide. Carbon monoxide not only substitutes itself for oxygen in the hemoglobin molecule but shifts to the left the oxyhemoglobin dissociation curve. This action, which is called the Haldane effect, increases tissue anoxia. Although the affinity of carbon monoxide for myoglobin is about five times lower than that of hemoglobin, the binding of carbon monoxide to myoglobin could play a role in explaining the symptoms of carbon monoxide intoxication by reducing the transfer of oxygen to the mitochondria of the muscle cells particularly in the myocardium. [A review of this subject has been presented elsewhere (190.)]

Other molecules can also bind carbon monoxide (like cyt. P 450), but the reduction of oxidative metabolism in vivo following carbon monoxide exposure has not been confirmed (218).

Repeated exposures to carbon monoxide can also modify the permeability of the blood vessel endothelium (12).

The biological TLV for carbon monoxide in blood is still controversial. There is currently enough evidence to suggest that the two organs most susceptible to carbon monoxide exposure are the central nervous system and the cardiovascular system. However the relationship between a slight elevation of the carboxyhemoglobin

level (e.g., from 1 to 5 %) and the occurrence of neurological or behavioral disturbances is not straightforward, and many investigations have given contradictory results. [A review of this subject has been presented elsewhere (98, 190).] The effect of acute carbon monoxide exposure on the myocardium seems well demonstrated, mostly in persons suffering from coronary heart disease. In these subjects a slight elevation of carboxyhemoglobin up to 5 % already exerts some deleterious effects (5, 8). This observation raises the important question of whether a biological standard should take into consideration persons already suffering from certain diseases. Personally I think that the answer should be positive when the disease has as high a prevalence as ischemic heart disease.

Furthermore animal experiments have demonstrated that in addition to its acute effect on the myocardium carbon monoxide may, after repeated exposures, favor the development of atheromatosis. The results obtained by Astrup's group in Copenhagen are so convincing that it has been suggested that carbon monoxide is the main atherogenic agent of cigarette smoke (12, 169, 353).

Since personal pollution by cigarette smoking is so prevalent, the observation leads to another important consideration, i.e., must work standards be more stringent than "environmental" standards? In the case of carbon monoxide I feel that the standard for industrial exposure should be developed to protect nonsmokers whatever the background exposure voluntarily tolerated by other workers because of their personal habits. In that case the maximum tolerable carboxyhemoglobin level in nonsmokers should be set at 5 %, which corresponds to the level reached after an 8-h exposure to 35 ppm of carbon monoxide (225).

Numerous methods have been published for the determination of carboxyhemoglobin [For a review of the literature the reader can consult Blackmore (34) and Lambert et al. (178).] The first group of methods requires the determination of the volume of carbon monoxide present in a known volume of blood. If the hemoglobin content of this blood is also measured, the carboxyhemoglobin level (in

the percentage of total hemoglobin) can be calculated since 1 mole of hemoglobin binds 4 moles of carbon monoxide. To this group of techniques belong the gasometric methods (55), the microdiffusion techniques with the reduction of palladium chloride (350), the gas chromatographic techniques (144), and the infrared absorption techniques (37).

The second group of methods includes the various spectrophotometric techniques from the most rapid and simple (359) to the most elaborate (294, 297). Unlike those of the first group, the spectrophotometric techniques allow a direct determination of the carboxyhemoglobin level without a preliminary determination of the blood hemoglobin content. My colleagues and I (45) have recently compared three different techniques for the determination of carboxyhemoglobin: (a) the microdiffusion technique of Vignoli et al. (350), (b) the infrared technique of Boudène et al. (37) and (c) the spectrophotometric technique of Commins and Lawther (56). Excellent correlations ($r > 0.99$) were found between the results obtained with the three techniques, but systematic differences were observed. This observation should be taken into account when results obtained by different techniques are interpreted.

CHROMIUM

The metabolism of chromium has not been extensively studied. After its absorption, mostly through the respiratory tract and to a lesser extent through the skin and the gastrointestinal tract, chromium is excreted quickly (14).

It seems that the chromium concentration in blood is not a valid index of exposure or body burden (16).

Chromium in urine appears to be more useful in the evaluation of exposure, but the information available on this subject is still very limited. The normal urinary chromium concentration is probably around 5 μg per liter (151). Franzen et al. (108) have proposed a maximal allowable concentration of 25 μg of chromium per liter of urine.

Techniques have been described for determining chromium in biological mate-

rials (68, 102, 123, 202, 251, 337, 340, 358), but the normal values reported in the literature must be interpreted with caution because chromium analysis has not yet been well standardized (59).

CYANIDES AND ALKYLNITRILES

Absorption of hydrocyanic acid, cyanides or compounds (e.g., aliphatic nitriles) that can liberate CN^- in vivo causes an increase of the thiocyanate concentration in plasma (257) and in urine (101). Since tobacco smoke contains HCN, it is normal to find a higher plasma concentration of thiocyanate in smokers (between 100 and 150 μmoles per liter, i.e., between 5.8 and 8.7 mg per liter) than in nonsmokers (between 20 and 50 μmoles per liter, i.e., between 1.2 and 2.9 mg per liter) (257). Elkins (92) places the normal urinary concentration of thiocyanate in smokers at approximately 9 mg per liter. No extensive survey of thiocyanate concentrations in the biological material of workers potentially exposed to cyanides has been performed, but because of the influence of cigarette smoking there is much doubt that these measurements may be of any value for following exposure under normal working conditions (101).

FLUORIDE

Fluoride appears rapidly in the urine after it has been absorbed (58). The urinary fluoride concentration is an excellent indice of fluoride intake (157). The current ACGIH TLV for fluoride is 2.5 mg/m^3 . It has been estimated that an 8-h exposure to such an ambient concentration would result in an absorption of approximately 5 mg of fluoride (142), corresponding to an end of shift urine fluoride concentration of about 4 mg per liter. Since osteosclerosis would not be expected in persons whose urine contains no more than 4 mg per liter (58), it is only necessary to ensure that the exposure conditions are such that the urinary excretion never exceeds 4–5 mg per liter (88). It should however be pointed out that the Soviet TLV is 1 mg/m^3 , which corresponds probably to a urinary fluoride

concentration of 2 mg per liter, and that advanced kidney disease has been shown to reduce the urinary excretion of fluoride (58).

The fluoride concentration in urine can be determined easily with the fluoride specific ion electrode (229, 318, 339).

HYDRAZINE

A fluorimetric method has been described recently for monitoring the plasma level of hydrazine (349). The level at which the biological threshold should be set is however unknown.

INORGANIC LEAD

The comparative merits of the various biological tests available for the evaluation of lead absorption have been often investigated (23, 61, 71, 116, 131, 182, 211, 289, 300, 332, 346, 355, 365, 373).

I intend to present only a brief account of the current thinking regarding the validity of these tests. The following comments only apply to adult workers and not to children (environmental exposure).

The various biological changes that develop following lead exposure and that have been proposed for the monitoring of workers can be classified schematically into two categories (182): (a) those which

Table 1. Biological changes that have been proposed for monitoring the exposure of workers to lead.

Evaluation of lead exposure or lead body burden	Evaluation of the biological action of lead
Lead in blood	Hemoglobin
Lead in urine	Hematocrit
Lead in urine after administration of a chelating agent	Stippled cells
Lead in hair	Coproporphyrins in urine
	Free erythrocyte porphyrins
	Porphobilinogen in urine
	δ -aminolevulinic acid (ALA) in urine
	ALA dehydratase in erythrocytes

not useful for monitoring workers exposed to lead because usually its increase does not precede the development of clinical signs of intoxication (116). This parameter is therefore not sensitive enough.

δ -aminolevulinic acid in urine. Because of the inhibition of δ -aminolevulinic acid dehydratase (ALA-D) by lead δ -aminolevulinic acid in urine (ALA-U) accumulates in the organism and is excreted in greater amounts.

Cramer and Selander (61) demonstrated that there is an excellent correlation ($r = 0.92$) between ALA-U and the amount of lead excreted in urine following treatment with penicillamine. They therefore concluded that ALA-U reflects the amount of metabolically active lead in the organism.

Several workers have also found a satisfactory correlation between ALA-U and Pb-B (61, 130, 191) or Pb-U (23, 71, 300). Following the administration of a chelating agent, ALA-U excretion also follows the changes in Pb-B (351).

A significant increase in ALA-U excretion occurs at approximately the same Pb-B level as coproporphyrinuria, i.e., 40 μg per 100 ml (191). The sensitivity of this test is therefore sufficient for detecting workers overexposed to lead.

It seems however that after the cessation of exposure Pb-B and Pb-U return faster to "normal" or "acceptable" values than ALA-U (278, 289).

The specificity of the ALA-U test is certainly better than that of coproporphyrinuria (24, 112, 300). Thus Basin (24) found, among 20 subjects suffering from various pathologic conditions (cirrhosis, acute ethylism, malignant hemopathies), a normal concentration of ALA-U but increased coproporphyrinuria excretion.

It is well known that a marked increase of ALA-U can also be found in acute intermittent porphyria (129) and in hereditary tyrosinemia (115), but the prevalence of these diseases is small.

In control individuals ALA-U does not exceed 4.5 mg per gram of creatinine. A concentration around 15 mg per gram of creatinine is a sign of overexposure to lead corresponding to a Pb-B of 70 μg per 100 ml (191).

Chromatographic (67, 212, 319, 364) and nonchromatographic (122, 183, 334, 352)

methods are available for ALA-U determination in urine. The validity of some of these techniques has been critically evaluated (272).

The acidified urine can be stored at room temperature in darkness for several weeks (272).

δ -aminolevulinic acid dehydratase. For the last 10 years the possibility of measuring the enzyme ALA-D directly has been considered since its inhibition (at least in critical tissues) is responsible for the excessive urinary excretion of ALA-U following lead exposure. Indeed one knows since the work of Lichtman and Feldman (203) that the erythrocyte enzyme ALA-D is inhibited by lead, and this observation has been confirmed by many authors (23, 35, 71, 72, 136, 137, 138).

ALA-D is highly sensitive to inhibition by lead (137). There is an excellent negative correlation between ALA-D activity and the concentration of lead in blood (with the Pb-B range 10 to 60 μg per 100 ml).

Depression of ALA-D activity in erythrocytes is not only a sensitive but also a specific index of exposure to lead since in workers occupationally exposed to two other heavy metals, i.e., cadmium and mercury, no reduction of ALA-D activity has been observed (184, 187).

It is interesting to note that ALA-D activity in human blood also decreases with the elevation of blood ethanol but returns to normal at the same rate as the ethanol level (219).

Until recently there was doubt whether the observed inhibition of ALA-D activity in peripheral blood by lead was an *in vivo* phenomenon or merely a result of membrane bound lead getting access to the intracellular enzyme as a result of hemolysis in the test tube required for determining ALA-D activity. In other words, the inhibition of erythrocytic ALA-D, as measured by the enzyme assay in test tubes, could be an *in vitro* artifact, reflecting only the concentration of lead in the circulating blood but not the true activity of this enzyme in the intact erythrocytes. My colleagues and I (273) recently demonstrated that the decrease of ALA-D in human erythrocytes measured under usual environmental and occupational exposure to lead ($\text{Pb-B} < 120 \mu\text{g}$ per 100 ml) is a

true reflection of the enzyme activity in vivo.

Contrary to the response of free erythrocyte porphyrins, depression of ALA-D activity following lead exposure occurs with no demonstrable time lag (332).

Although there is no doubt that ALA-D is currently the most sensitive indicator of lead effect, quickly followed by FEP, its high degree of sensitivity (no threshold below which the enzyme is not inhibited) and the technical problem raised for its correct determination (in particular conservation of the blood sample at 0°C for a limited time interval) (30) limits its usefulness for the monitoring of workers.

In summary I recommend two tests for the routine monitoring of lead workers: Pb-B and ALA-U (which is more specific than coproporphyrinuria). The first (Pb-B) reflects the absorption of lead and the second (ALA-U), its biological action. When only one test must be selected, I recommend ALA-U, which evaluates exposure and effect, is simpler to perform accurately than Pb-B, and does not entail any risk of sample contamination. It should be kept in mind that these recommendations only apply to the monitoring of workers and not to the evaluation of environmental exposure to lead. In the latter case more sensitive tests (ALA-D, FEP) than ALA-U should be preferred.

TETRAETHYLLEAD

Pb-B concentration is not a good index of tetraethyllead absorption. It is suggested to follow workers exposed to alkyllead derivatives by measuring lead in urine (Pb-U) (104). The American Industrial Hygiene Association has proposed the following criteria (Hygienic Guide Series 1963): Pb-U: > 0.11 mg per liter: exposure is above normal; Pb-U: 0.15 mg per liter: the worker should be moved to an area of less exposure.

This proposal seems logical since Foa et al. (105) always observed Pb-U levels in excess of 200 µg per liter in cases of intoxication by tetraethyllead.

The activity of the blood enzyme ALA-D is also reduced in men working with lead alkyls (217).

MANGANESE

Manganese-loaded subjects do not excrete significant amounts of manganese in the urine (60, 207). Fecal elimination, probably following biliary excretion (54, 171, 330), constitutes the main route of manganese excretion in man (207). The usefulness of analyzing urine for manganese as a means of evaluating occupational exposure is therefore doubtful. However Tanaka and Lieben (327) found that on a group basis the urinary manganese concentration of exposed workers shows a rough correlation to the average air concentration. Normal adults excrete between 1 and 8 µg of manganese per liter of urine. Since EDTA has been shown to mobilize manganese and to increase its urinary excretion (252, 360), analysis of urine after EDTA administration could be useful to confirm the existence of an increased manganese body burden. Further work is however required to confirm the validity of this test.

Jonderko and his collaborators (155) found a significant correlation ($r = 0.50$) between manganese in serum and the duration of employment in a manganese alloy foundry. They proposed 20 µg per 100 ml of serum as the threshold value of manganese retention. They found however that the increase in manganese concentration in blood appears at the earliest after 4 years of exposure and quickly falls when exposure is ended even in workers with signs of poisoning. Penalver (252) expressed doubts about the usefulness of manganese determination in blood. Furthermore Mahoney and Small (206) reported that manganese is rapidly cleared from the plasma and reappears bound in red cells. It would therefore be more logical to measure manganese in whole blood rather than in serum.

The feasibility of measuring blood manganese levels as an index of exposure should deserve further investigation.

In summary no valid biological test can yet be proposed to evaluate manganese exposure although manganese determination in stools has been suggested by a Soviet worker (154).

Techniques have been proposed for determining manganese in biological samples (47, 53, 207, 324, 331, 345).

INORGANIC MERCURY

The determination of total mercury in urine is routinely used as a means of evaluating the extent of exposure to mercury vapor. It is recognized that there are significant interindividual variations in mercury excretion in urine, but several investigations have demonstrated that on a group basis the biological factor reflects the importance of mercury exposure (93, 127, 156, 186, 266, 298). The allowable concentration of inorganic mercury in urine of exposed workers is still unsettled. Elkins (92) suggested the value of 200 to 250 μg per liter. The relationship between mercury concentration in air and urine obtained by Smith et al. (298) indicates that this excretion would result from an average exposure to 0.1 mg/m^3 . The ACGIH TLV for mercury vapor has however been recently reduced to 0.05 mg/m^3 , which on the basis of Smith's finding (298) corresponds to a urinary concentration of approximately 100 $\mu\text{g}/\text{liter}$. Other data (186) suggest however that the urinary excretion of a group of workers exposed to 0.05 mg/m^3 would be lower and probably closer to 50 μg per liter than 100 $\mu\text{g}/\text{liter}$. The observations are in perfect agreement with those of Bell et al. (27), who found that the air/urine relationship (mg/m^3 and mg/liter) approximates 1 to 1. It was therefore recommended (186) that, if a group of workers exposed to inorganic mercury excretes more than 50 $\mu\text{g}/\text{l}$, corrective industrial hygiene measures should be initiated. The California Bureau of Occupational Health reached the same conclusion. It should be stressed that several factors may influence the results of mercury measurement in urine, and serious consideration should be given to them when interpreting the results, i.e., (a) the reliability of the analytical method selected as used by the laboratory (57, 192), (b) the risk of urine contamination when instructions are not given to employees (hand washing, work clothes removal, etc.) before voiding specimens, (c) loss of mercury by volatilization when bacterial growth is not prevented during storage (204) or by adsorption on the container wall (338), (d) the existence of other sources of mercury exposure than the occupational ones, e.g., the use of mercurous

chloride as a laxative (69), skin application of mercurial preparations (antiseptic soap, cosmetics, etc. (22, 209, 341) and recent dental filling. The failure to recognize the influence of these factors, as well as the difficulty to evaluate correctly the time-weighted average exposure (25, 26), may explain the apparent lack of correlation between the degree of exposure and the urinary concentration of mercury for a single worker.

Recently it has been proposed (135) to measure separately elemental mercury, stannous-chloride-reducible (ionic) mercury, and total mercury in urine (elemental, ionic but free and bound mercury). The hypothesis behind such a proposal is that, as long as the rate of exposure does not exceed the rate at which the body can oxidize mercury and excrete it in the urine in a bound form, the rate of exposure appears to have a margin of safety. This hypothesis deserves further research work.

ALKYLMERCURY DERIVATIVES

The urinary output of mercury is not a very useful index of alkylmercury compound exposure, which represents more of an environmental hazard than an occupational one.

On the other hand blood mercury concentration is a better index of the body burden of alkyl mercury derivatives (15).

An international committee of experts (267) has proposed that the blood mercury concentration in individuals exposed to ethyl and methyl mercury compounds should not exceed 10 μg per 100 ml, but according to Skerfving (296) neurological manifestations can already occur at this level.

NICKEL CARBONYL

The normal average values for nickel concentration in urine reported in the literature are quite variable and range from 2.3 to 40 μg per liter (151, 168, 214, 235, 256, 320, 322, 335). Sunderman (323) proposed that workers be treated with the chelating agent sodium diethyldithiocarbamate when nickel concentration in urine exceeds 100 μg per liter. The American Industrial

Hygiene Association (4) considers that urinary concentrations below 0.25 mg per liter indicate a mild exposure and that urinary concentrations above 0.5 mg per liter suggest a severe exposure.

Spectrophotometric (220, 321) and atomic absorption procedures (235, 283, 320) have been described for measuring nickel in biological material.

SELENIUM

Reviewing the early literature data on selenium, Patty (250) concluded that its urinary excretion parallels intake. Therefore selenium in urine is a valid test of exposure. The average concentration in persons not occupationally exposed is 0.03 mg per liter (128, 301). For workers a biological TLV of 0.1 mg/l has been proposed (250).

THALLIUM

It is well known that acute and chronic intoxication by thallium can be confirmed by measuring its urinary concentration (32). To my knowledge the biological TLV corresponding to a time-weighted average exposure of 0.1 mg/m³ (ACGIH 1974) has not been determined.

INORGANIC TIN

It has been suggested that the urinary concentration of tin can give a rough estimate of the amount absorbed (141, 161, 284), but, since inorganic tin is not an important industrial hazard, not much effort has yet been devoted to studying extensively the relationship between occupational exposure and the concentration in biological material.

Schroeder et al. (284) estimated that the normal urinary excretion of tin in man ranges from 0 to 40 µg/24 h (average 23 µg/24 h).

VANADIUM

Some reports have indicated that exposure to vanadium results in an increased concentration of the metal in urine and/or in

blood (153, 201, 295). Lewis (201) examined 24 men exposed to vanadium for more than 6 months (atmospheric concentration of vanadium from 0.097 to 0.925 mg/m³). The mean urinary concentration of vanadium in these workers was 46.7 µg per liter against 11.6 µg per liter in a control group. Sjöberg and Rigner (295) also observed an increased blood and urine vanadium concentration in workers who had been exposed to vanadium pentoxide.

Zenz and Berg (372) exposed volunteers to 0.2 mg/m³ vanadium pentoxide for 8 h and detected an increased urinary concentration of vanadium which was maximum 3 days after exposure. Not enough information is available however to conclude whether vanadium concentration in urine is correlated with air concentration, and therefore no biological TLV can yet be proposed for this parameter.

Mountain (221) and his colleagues also proposed to determine the cystine content of the fingernails, which decreases with chronic exposure to vanadium.

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