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BENZENE: THE INTERPRETATION OF MONITORING RESULTS

R. J. SHERWOOD

Esso Europe Inc.

Abstract—This paper considers the practical evaluation of the exposure of workers to benzene vapour. It is principally concerned with relating the results obtained from modern sampling techniques to the current criteria for assessing the hazard. The three aspects considered are: sampling the air the man breathes while at work; measuring benzene in the breath he exhales after work; and determining increase in phenol content of his urine.

The relationship of these measurements is discussed and the need to develop a mathematical model for describing benzene retention in critical organs of the body, and its subsequent elimination, is indicated.

INTRODUCTION

BENZENE (C_6H_6) has been recognized as a toxic chemical causing chronic poisoning since 1897 (HUNTER, 1962), and over the years a very comprehensive literature on its industrial toxicology has developed. Published information on human exposure is principally restricted to pathological studies on poisoned men, though metabolism and toxicology has been extensively studied in experimental animals.

As reliable data on occupational exposure are scarce, little of this literature is of immediate value to the industrial hygienist. In many cases no information is available, in others it is based on a few "environmental" measurements which may give no real indication of true exposure.

Recent steps (COUNCIL OF EUROPE, 1959) to the legislative control of the benzene hazard* have principally restricted the benzene content of industrial solvents. This has been based on technical feasibility of obtaining such solvents, rather than on a toxicological threshold.

As the relationship between workers' exposure and concentration of benzene in a solvent depends on many factors, and may vary over many orders of magnitude, there appears to be no inherent danger in using a solvent containing (for example) 10 per cent benzene, nor inherent safety in using one containing 1 per cent. Only by systematic measurement of exposure during the use of substances containing benzene can hazards be properly assessed.

Although such controls have a beneficial effect in reducing overall exposure to benzene (as no doubt does the confirmation or reduction of threshold limit values—which are seldom actually applied in industry), they cannot be considered totally adequate as a means of economically controlling benzene hazards.

It is essential that, coupled with techniques for identifying susceptible individuals,

* Subsequent to the Symposium, a Convention has been published (INTERNATIONAL LABOUR OFFICE, 1971) on protection against benzene, which treats all products containing more than 1 per cent benzene (by volume) as pure benzene.

information on industrial exposures and workers' pathology should be obtained to enable a damage risk criterion to be established. This should take the form that the annual risk of serious illness (or death) to a non-susceptible individual should not exceed a prescribed value (at this time in the U.K. it might be set at 10^{-4} or 10^{-5}). Criteria for non-occupational exposure might be of the same order but equally applicable to susceptible individuals. If the methodology discussed here were applied wherever men may be exposed to benzene, and adequate exposure and medical records were kept, such criteria could be established.

In the following review of the application of present techniques, the Author has drawn mostly from his own work (SHERWOOD and CARTER, 1970), as he is familiar with its derivation. He does not wish to imply that similar and more important work is not being undertaken elsewhere. In particular, attention should be drawn to a meeting of experts on the safe use of benzene and solvents containing benzene (INTERNATIONAL LABOUR OFFICE, 1968).

AIR SAMPLING

Personal air sampling for benzene vapour can provide a quantitative index of a worker's exposure. Slight errors may arise from spatial separation of the sampling head from the nose and mouth. But this can be minimized by shoulder mounting of the sampler. Larger uncertainties may arise when relating this to possible intake of benzene as the individual's breathing rate and the proportion retained are usually unknown. Although these factors are important if the toxicity of benzene is to be determined, they are not involved in assessment of exposure by application of threshold limit values, though it must be appreciated that the latter are generally derived from measurements with a limited number of fixed position samplers that may not provide a true measure of exposure of any individual.

In the derivation of safe threshold limits from occupational studies, it is common practice to calculate mean values of an appropriate biological parameter for a group of workers, and to relate thir lo an estimated environmental concentration of the mated in air. This technique should be regarded as suspect, as it should only be applied where exposure is shown to be identical for all members of the group. In the Author's experience such situations are rare and it is usually necessary to assess each individual's exposure separately.

An initial problem facing a hygienist is that air concentration criteria are too many rather than too few. Values of threshold limits ranging from 100 to 6 ppm have ban reported (INTERNATIONAL LABOUR OFFICE, 1968). In the United States alone, values from 100 to 10 ppm having different applications are recommended by three authorities (AMERICAN NATIONAL STANDARDS INSTITUTE, 1969; AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS, 1971; AMERICAN INDUSTRIAL HYGIENE ASSOCIATION, 1970), though the recently enacted Occupational Health and Safety Act (1971) prescribes that the ANSI standard takes precedence. This specifies an acceptable maximum for peaks of 50 ppm: a ailing concentration of 25 ppm, and a time weighted average of 10 ppm.

The interpretation of air sampling results has been discussed elsewhere (SHERWOOD, 1971a; JONES and BRIEF, 1971), and will only be summarized here.

Results from any series of air sample measurements can be described by a probability distribution, and this is commonly found to approximate to the logarithmic

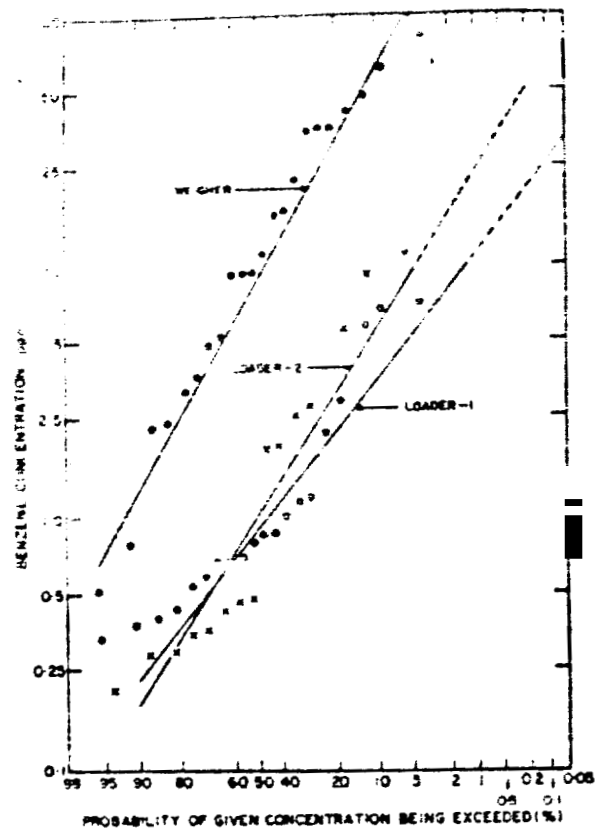

FIG. 1. Log-probability plots of air sampling results.

normal (see Fig. 1). As there is a finite possibility of exceeding any given concentration up to saturation of vapour in the air, it is not possible *to* apply any absolute upper limit below that concentration.

However if it is accepted that not more than one 10-minute sample may exceed 25 ppm, then (as there are 48 such samples in an 8 hr working day), the probability of exceeding 25 ppm should be *limited to* about 2 per cent. Thus, criteria for safe exposure are that the average concentration over *the* working day should not exceed 10 ppm. and that the probability of exceeding 25 ppm in any 10-min period should not be more than 2 per cent.

Some personal air sampler measurements of exposure *to* benzene vapour during the buik loading *of* petrol, which commonly contains 3–6 per cent benzene, are shown in Tnbk 1.

Although generalization cannot be made from so few results, they do show that none of the operations studied led to the daily time weighted average limit of 10 ppm being exceeded, and that only drivers loading road tankers exceeded the short term criteria during the period of loading. As drivers do not normally spend more than about one half-hour per shift loading their vehicle, the probability of the ceiling value

TABLE 1 EXPOSURE DURING [illegible] OF PETROL

Operation	Man exposed	No. of operations studied	No. of samples	Observed values: Arithmetic mean (ppm)	Observed values: Probability of exceeding 25 ppm (%)	Normalized to an 8-hr working shift: Arithmetic mean (ppm)	Normalized to an 8-hr working shift: Probability of exceeding 25 ppm (%)
Barge loading	Captain	1	5	4·3	1·4	0·8	0·3
Road loading	Driver	14	36	1·1	3·0	0·2	0·2
Rail loading	Loading arm operator	5	6	1·0	0·01	1·0	0·01

criteria being exceeded was about 0·2 per cent over the whole shift period. The high exposures measured at one particular rail loading rack have been excluded from this data, as the operation is exceptional, and has been reported separately. (SHERWOOD, 1972) A programme of measurement continues and more definitive information will be available in time.

This form of analysis has also been applied to the data collected in a survey on car filling sponsored by the Institute of Petroleum (PARKINSON, 1971). At typical retail filling stations it was found that the probability of 25 ppm being exceeded was much less than 0·01 per cent, while mean concentrations varied from 0·3 to 2·4 ppm.

Proposed new criterion

This type of evaluation is laborious and can only be undertaken as a special investigation. However, routine monitoring of all benzene workers should become economically feasible, as it has been shown (SHERWOOD, 1971b) that in practice the proposed criteria can be met by setting a limited daily exposure dose of 5000 ppm-mrn (that is, the multiple of concentration in ppm and exposure time in minutes should not exceed 5000), independent of time from a few minutes to an 8-hr working day. The application of such a criterion avoids the complications that arise in interpreting mutts against a 25 ppm ceiling value, and the need to restrict duration of each sample to 10 min.

Further, it would permit the construction of a simple personal air sampling instrument requiring only a single sample for each shift worked by each man.

Large numbers of men could be monitored in this way and, if samples are analysed at a central laboratory, automatic gas chromatographic equipment would prove economic.

Threshold limit values are generally the only legislated or recommended numerical criteria available. While criteria have been proposed for benzene in breath and phenol in urine, they are not well established. It is, therefore, essential that international agreement be reached on an acceptable value, and a daily exposure dose of 4000 ppm-min (which corresponds to a time weighted average slightly over 8 ppm for an 8 hr day) is proposed by the Author.

This limit would not carry much greater biological risk than the USSR limit

(INTERNATIONAL LABOUR OFFICE, 1970) of 20 mg m³ (6·3 ppm) or significantly greater economic penalty than the U.S.A. limit of 10 ppm, it has the advantage of being independent of working time.

If this value is accepted, then a sound long-term international objective would be to determine the risk arising from exposure at this level.

EXHALED BREATH SAMPLING

Sampling of exhaled breath after exposure to benzene vapour indicates the rate at which benzene is being directly eliminated from the body, from which it may be possible to deduce the quantity absorbed.

Immediately after exposure, the concentration in exhaled breath drops rapidly, but the rate of change lessens later (HUNTER, 1968). It is reasonable to surmise that the process can be represented by storage in a series of compartments within the body, elimination from each being adequately described by an exponential function. Thus, at first benzene is rapidly lost from the circulating blood, next, the principle contribution may come from muscular tissue, and finally, the slow component comes from fat.

If the exposure period is short, then little benzene reaches muscle or fat, and elimination will be characterized by a single rapid period of release. If the exposure period is long, then a greater proportion of the total will be released only slowly. In practice, industrial exposure is commonly not constant with time, and absorption and elimination processes are in continuous dynamic change.

If exhaled breath measurement is to be applied as a routine method of monitoring men exposed to benzene, only two opportunities for sampling exist—immediately after each shift and immediately before the next. End of shift sampling provides the most sensitive method of assessing exposure as the rate of elimination is likely to be high. However, unless the exact time and duration of exposure are known, the results are barely quantitative, as exposure towards the end of the shift is detected with a much greater sensitivity than that near the beginning.

Pre-shift sampling suffers considerably lower sensitivity, but is far more quantitative as the elimination rate changes only slowly at that time. It provides a measure of the longer retained components and may therefore be a good index of the risk of chronic disease. Disadvantages are the greater skill required for analysis at the low concentrations to be measured, and the risk of interference from non-occupational exposure to benzene.

The two field methods developed for sampling exhaled breath are breath sampling tubes and the breath sampling respirator. The former have advantage of instantaneous collection, complete absence of chemical pretreatment before gas chromatography, and ready collection of duplicate samples. Although the latter requires a 10-min sampling period for each operator, it provides a more consistent measure of elimination, as all exhaled breath over the period is sampled, and it reduces the risk of interference from ambient benzene vapour.

The respirator method is better suited for special investigation of exposure, and the sensitivity can be increased considerably over the method as published (SHERWOOD and CARTER, 1970), while breath sampling tubes could be more suitable for routine assessment. For routine monitoring, samples are best taken at the end of the shift and analysed promptly, so that any follow-up samples needed can be taken before the next shift commences.

Criteria

Criteria for assessing exposure have been published (Sherwood, 1972) and further experience does not suggest the need for serious amendment. Currently applied values are:

(1) shortly after exposure to 25 ppm ... about 2 ppm in breath
(2) 16 hr after exposure to 100 ppm-hr ... 0·2 ppm in breath

The first criterion assumes that samples are unlikely to be taken until at least one half-hour has elapsed so that the initially high benzene concentration in blood has been lost; it is of low accuracy.

Elimination from one subject is shown in Fig. 2, after experimental exposure of

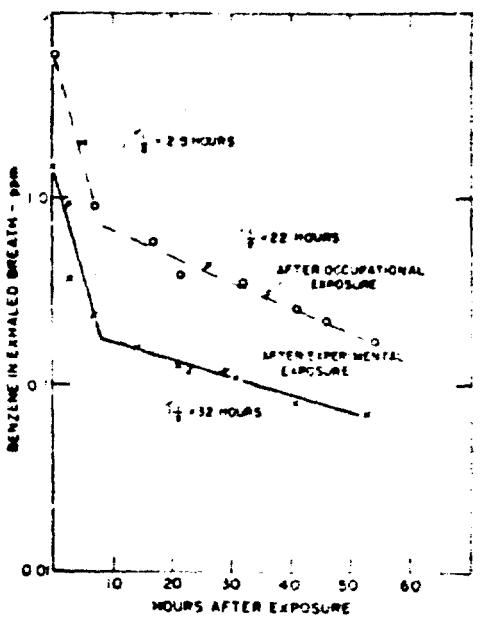

FIG. 2. Elimination of benzene in exhaled breath of one subject after experimental and occupational exposure of about 4 hr duration.

4·5 hr duration, and after a complex pattern of exposure lasting about 70 hr on board a ship carrying benzene, the principle exposure occurring in the last 4 hr.

Two compartments appear to be present; the first with a half-life of about 2·5 hr, and the second with a half-life of about 1 day.

If a special investigation of an individual's exposure has to be made, a series of samples taken after exposure has occurred might indicate, from the relationship of the concentration measured and its rate of change, the magnitude of the exposure. Thus, a rapid fall in concentration over a period of a few hours would indicate that recent exposure had occurred; a slow fall would indicate considerably greater exposure in the more distant past.

PHENOL IN URINE ANALYSIS

This is currently the most commonly used technique for determining the quantity of benzene being metabolized in the worker's body. It may also be the best index of hazard, but the toxic action of benzene in the body is not sufficiently understood for this to be certain.

The metabolism of benzene in the body has been well elucidated by WILLIAMS (1960) from animal experimentation, and distribution in the body of the dog has been explored by SCHRENK *et al.* (1941). It has been assumed that a similar pattern occurs in humans. That part of the benzene which is taken into the body and not exhaled is largely converted in the liver to phenol, and this is detoxified by conjugation with sulphate or glucuronide and excreted in urine. Relationships of exposure and phenol excretion have been thoroughly reviewed by DOCTER and ZIELHUIS (1967).

The earlier biological monitoring method of determining the ratio of ethereal to inorganic sulphate is less sensitive. Although it detects the same mechanism, normal excretion of sulphate is far greater than, and more variable than that of phenol. Colorimetric methods of analysing phenol vary in their specificity, and all suffer interference from one or more cresolic compounds which may be naturally present.

Procedures for hydrolysing the conjugated phenol have been the subject of controversy as it has been shown that very strong acids are required to free phenol from the glucuronide conjugate, but this process may destroy free phenol already present. Reasonably good correlation between results using strong and dilute acid methods applied to field samples has suggested that phenol glucuronide *is* not commonly present.

A series of samples from exposed men was hydrolysed by more specific methods and the results are shown in Table 2.

The sum of phenyl sulphate and phenyl glucuronide frequently exceeds the total assessed by the perchloric acid method. Measurements of free phenol made on samples 3 and 4 only showed 16 and 70 mg/l, respectively, which *is* insufficient to account for the difference. Slightly incomplete hydrolysis by perchloric acid, or partial destruction of phenol are possible causes. The results show that phenyl sulphate is *the* major metabolite excreted by the men measured, but the proportion of glucuronide excreted may rise at high (>400 mg/l) total concentration.

While hydrochloric acid hydrolysis may be suitable for a screening test, it appears necessary to use perchloric acid for quantitative assessment of high values. Close

TABLE 2. DETERMINATION OF PHENOL CONJUGATES IN URINE

Form measured:	Total phenol	Phenyl sulphate	Phenyl glucuronide
Hydrolysis method: Sample No.	Perchloric acid (mg/l)	Hydrochloric acid (mg/l)	β-glucuronidase (mg/l)
1	54	57	7
2	88	110	5
3	418	415	109
4	1000	954	349
5	363	362	32
6	163	109	2
7	69	83	10
8	38	44	2

petrol. Piotrowski (1971) has shown a half-life of 3·4 hr for urine elimination after exposure to phenol vapour.

Comparison of these elimination rates with those of benzene in breath suggests that the rate of elimination of phenol in urine is, perhaps, controlled by the rate of metabolism in the liver.

More detailed studies of elimination of phenol and other excreted products, and their relationship to benzene concentrations in breath, might provide a better understanding of the behaviour of benzene in man, but there may be need also for determination of benzene concentrations in venous blood.

A feature in Fig. 3 which appears commonly is a marked rise in concentration of phenol after elimination has fallen to a low value. The significance of this is totally unknown, but it could mark the end of the mobilization of the defensive conjugation process. The analytical procedure is sufficiently specific for it not to be the elimination of catechol and quinol.

Although no information on natural phenol levels has been obtained, detailed assessment has been made of results from a group of workers over a one-year period. The overall data fit a log-normal distribution having a median value of about 8 mg/l, and a geometric standard deviation of about 2·5. The number of samples from any one individual is insufficient for statistical analysis but the total data suggests that concentrations over 30 mg/l may represent benzene exposure, and that for some men exposure may be suspected if a sample exceeds 20 mg/l. For 33 per cent of the men, no sample during the year exceeded 20 mg/l and 70 per cent of this low level group showed a minimum concentration below 5 mg/l.

If a group of unexposed individuals were sampled over a period, it should be possible to determine more precisely the probability of any individual exceeding a given concentration. Analysis of data from benzene workers can reveal occasions when significant exposure has occurred, but concentrations at the upper end of the "natural" range are difficult to interpret. A combined programme of urine and exhaled breath analysis would provide far more information on natural phenol levels as well as identifying exposure events.

Criteria

In the United Kingdom, a biochemical threshold limit of 100 mg/l has been proposed (1969 REPORT OF CHIEF INSPECTOR OF FACTORIES, 1970). This is in the same range as the criteria already proposed (SHERWOOD, 1971b):

1. Immediately after exposure to 25 ppm in air . . . 100 mg/l
2. 16 hr after exposure to 100 ppm-hr . . . 50 mg/l.

Further experience is necessary before a reliable criterion can be deduced for samples taken at the end of a shift exposure to 4000 or 5000 ppm-mrn with concentrationr having geometric standard deviations varying from 1·5 to 4·5.

Working guide lines for the management of a routine urine monitonng programme have been prepared and are shown in the Appendix.

COMPARISON OF CRITERIA

In field sampling for operational investigations it has proved difficult to obtain data to confirm the relationships of the three systems of measurements, but some limited information that has been obtained is shown in Table 4.

correlation between perchloric acid hydrolysis and the on-column-method using phosphoric acid (HARRIES and SH[illegible], 1965) has already been reported.

Adequate preservation of urine samples by the addition of 2–3 drops of toluene and storage at normal refrigerator temperature (5 C) is shown in Table 3. Although

TABLE 3. STABILITY OF PHENOL IN REFRIGERATED URINE

Sample No.	Phenol concentration (mg/l) Initial analysis	Analysis after 1 year
1	4	4
2	54	72
3	106	130
4	363	470
5	730	790
6	1020	1400

some changes occur, they would not seriously affect the interpretation of the results.

Interpretation of analytical results for phenol in urine is made difficult by a number of factors. Phenol itself is normally present in urine in small and variable amounts, but it is believed that a few individuals may normally excrete concentrations which approach the criterion for exposure control. Certain foodstuffs and drugs may also increase phenol excretion, as will exposure to phenol. For example, a concentration of 100 mg/l was detected about one half-hour after accidental skin contamination by phenol which was rapidly treated. The concentration fell to 50 mg/l 1 hr later, and was down *to* 23 mg/l 3 hr later. This suggests a half-life in the body of 1–2 hr, which can be compared with that observed after experimental and occupational benzene exposure of one subject (see Fig. 3), which was of the order of 6 hr, a value which also describes the overnight excretion from workers employed on bulk loading of

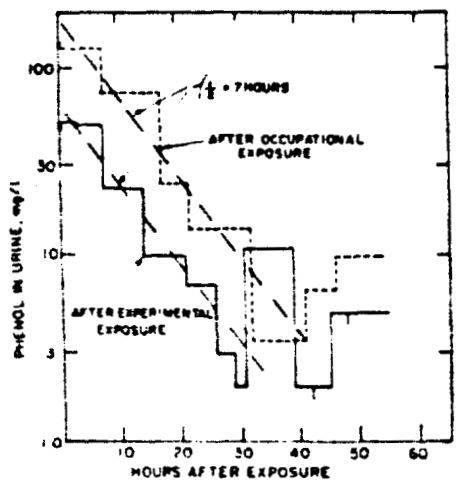

FIG. 3. Elimination of phenol in urine of one subject after experimental and occupational exposure of about 4 hr duration.

Using the criteria previously proposed (see above), exposures have been calculated from observed breath and urine measurements, and are compared with the measured air concentrations. It can be seen that there is generally agreement within a factor of 2.

TABLE 4. CALCULATION OF BENZENE EXPOSURES FROM MEASUREMENTS IN BREATH AND URINE

Operation	End of shift measurements			Measurements after 16 hr		
	Measured concentration (ppm)	Concentration calculated from Breath (ppm)	Concentration calculated from Urine (ppm)	Measured exposure (ppm-hr)	Exposure calculated from Breath (ppm-hr)	Exposure calculated from Urine (ppm-hr)
Gasoline rail loading						
Loader 1	2·0	1·8	2·2	—	—	—
Loader 2	2·7	2·4	3·8	—	—	—
Weigher	8 to 12	14	18	110	70	80
Gasoline barge loading	7	8	—	—	—	—
Benzene barge loading	20 to 70	50	50	430	—	440
Experimental benzene exposure	25	20	13	110	100	50

A MATHEMATICAL MODEL FOR BENZENE IN THE BODY

The hazards of ingesting or inhaling radioactive substances have been primarily assessed from the construction of a mathematical model (INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, 1959), and such a technique has been used *to* estimate uptake and elimination of anaesthetic gases (PAPPER and KITZ, 1963).

Experimental and occupational exposure to methylene chloride has thus been described with a compartmental model by RILEY *et al.* (1966). Conversion of benzene to phenol and its elimination must be taken into account and this process has been described for a drug compartmental model by SCHNEIDER (1970).

As industrial exposure to benzene vapour is typically highly variable, estimation of the burden of benzene in the body, or in such critical organs as brain or bone marrow, is only possible if computer techniques are employed. MAPLESON (1963) describes an analogue computer for common anaesthetic gases, but digital techniques would now be preferred.

Such calculations require information on the uptake and release of benzene from body organs which is not available for man. However, estimates can be made from a knowledge of the blood perfusion of the organs, and the partition coefficients for benzene in blood and *the* various tissues.

Partition coefficients

As no published information could be traced for the solubility of benzene in fat, simple range finding experiments for both blood and olive oil (representing fat) how been made.

Samples of chelated whole blood from the experimental subject, and of olive oil were injected with small quantities of benzene and, after allowing to equilibrate for a long period at 37°C, the benzene concentration in the vapour space over the samples was determined, and the Ostwald partition coefficients calculated.

Blood to air coefficients of 0·032 were determined for benzene concentrations in blood from 10 to 10,000 ppm. the corresponding coefficient for olive oil to air was found to be 3·1.

The value for benzene in blood is similar to the value of 0·023 that can be calculated from SCHRENK *et al.* (1941) or of 0·027 deducible from TEISINGER and SKRAMOVSKY (1947). If these values are inserted directly into the equations of MAPLESON (1963), expected elimination half-lives from muscle and fat would be 15 min and 50 hr. These are not in accord with the values of 2·5 hr and about 24 hr calculated from the exhaled breath observations and further investigation is evidently required. No allowance has, for example, been made for metabolism of the benzene in the body and this could well significantly affect prediction of the long-term component.

Computer programme

To permit better evaluation of critical organ burdens, a digital computer programme has been prepared (NICE, 1971) and it is hoped at a later stage to incorporate into the programme the varying concentrations met in occupational exposure. If the numerical results are in accord with observed values in the field, this technique should provide useful information on the probable benzene burdens in critical organs during and after occupational exposure and would, for example, permit assessment of the relative biological significance of the 10 ppm time weighted average and the 25 ppm ceiling threshold limit.

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APPENDIX

MONITORING OF BENZENE EXPOSURE
KEY POINTS FOR ROUTINE ASSAY OF PHENOL IN URINE

Programme should be prepared by management and medical department: privacy of results to be controlled by medical department. Gas chromatographic technique to be used requires technical skill. Ensure adequate liaison between analytical and medical departments.

Collect samples at end of shift: continuous follow-up with men will be needed to ensure full response.

Start programme with two-week sample periods for all men who may be exposed to vapour from products containing >10 per cent benzene. Modify programme as necessary once high or low risk groups or individuals have been identified.

Values over 100 mg/l indicate significant risk.

Values over 30 mg/l probably indicate benzene exposure.

Values less than 10 mg/l show all is well.

Values between the limits are ambiguous. To investigate, collect samples before and after work and look for any increase. Some foods and drugs produce phenol in urine, as does phenol inhaled or on the skin.

If high natural values are suspected take samples before work starts after longer break (weekend or vacation).

Whenever a high concentration is detected, take further sample immediately—preferably before next shift. If still high, trace cause and continue frequent sampling until levels drop.

Initially use 100 mg/l as criterion: reduce to 50 mg/l when possible. In long term, use values more than 2 × standard deviation above mean or median for each individual if these are below 50 mg/l.

If individuals in one group are consistently low, drop to monthly sampling.

As exposure may not be detectable after 24 hr, arrange programme to cover periods when exposure is likely.

Require special samples if accident is suspected or where exposure may have occurred (include requirement on special work permits). Reject results if specific gravity is below 1 010. If such a sample show more than 30 mg l, take second sample.

When programme has settled, check also men who may have routine exposure to products containing 1-10 per cent benzene.

Further monitoring for this group depends on results actually obtained.

After about 1 year, apply statistical methods to assess risk of significant exposure and to control future programme.

Benzene is a chronic poison: pay attention to long-term exposure conditions. One high result is probably not so significant as two or three results at lower level—these show that investigation and improvement is required.

Personal air sampling and exhaled breath measurement are also important techniques; the first is more sensitive, the second more specific, than urine analysis.

Legislative standards generally refer only to air sampling.