IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Environmental Concentrations

Historically, high atmospheric concentrations of organic solvents existed in the working environment principally due to the lack of knowledge of solvent toxicity, of hazards associated with solvent use, and the lack of enforcement of proper engineering controls. The problem was most serious during the winter months when doors and windows of plants were closed, thus preventing adequate ventilation. Although improvements in conditions have been made through substitution of solvents and incorporation of adequate ventilation design, the problem still exists in varying degrees. As recently as 1967, Longley et al [25] reported an incident involving a total of 29 men being exposed to high concentrations of toluene. Due to inadequate ventilation, levels of toluene rose to an estimated 10,000 to 30,000 ppm rendering 2 men unconscious while spraying a toluene-containing insecticide inside the hold of a merchant ship. Two hours after the incident, the toluene concentration was measured and indicated a range of 5,000-10,000 ppm. When one considers that the lower flammable limit of toluene is 12,000 ppm, the hazard encountered was not only a health hazard but also one of fire or an explosion.

In 1971, Forni et al [38] reported results of a study initiated in 1953 in a rotogravure plant. Toluene was substituted for benzene

in that year following an epidemic of benzene poisoning in the plant. From 1954 to 1956, the concentration of toluene ranged from 0 to 240 ppm in different parts of the work areas. Tabulated results of toluene concentrations from 1957 to 1965 indicated an annual mean value of 203 ppm (range, 140-239 ppm) at the center of the room, 203 ppm (range, 56-277 ppm) near one of the folding machines, and 431 ppm (range, 306-824 ppm) between the machine elements. In 1966, the plant was moved and improved ventilation was installed such that in 1967, the annual mean concentration of toluene was 156 ppm near the folding machines and 265 ppm between the machine elements.

Ikeda and Ohtsuji [59] in 1969, during a study of hippuric acid excretion in the urine of workers, reported on toluene concentrations in 11 workshops in 8 factories operating polychromic rotary processes for photogravure printing. Concentrations of toluene ranged from 4 to 240 ppm in the 11 workshops.

Pagnotto and Lieberman [60] in 1967 reported the results of their study of exposures to toluene in 11 leather finishing and rubber coating plants. In leather finishing, toluene was an ingredient in thinners used to prepare lacquers and stains that were automatically sprayed on leather with mechanical exhaust ventilation in operation. Toluene concentrations ranged from 19-85 ppm, averaging 53 ppm, in the finishing area. The highest exposures were found in washing and topping operations where leather was washed with a thinner and the finish applications were performed by hand with a gauze sponge. At

the washing and topping operation, an average value of 112 ppm was found (range, 29-195 ppm). In the rubber coating plants, toluene exposure occurred when rubber, prepared with petroleum naphtha (less than 1% benzene and 8% toluene), was applied to fabric as it was unrolled on a spreading machine. Some plants used pure toluene in the rubber preparation. Concentrations of toluene averaged 73 ppm at the spreading machines (range 34-120 ppm) at the 11 plants.

The aircraft industry has used large amounts of toluene as a component in paints. In 1942 Greenburg et al [37] reported ineffective local exhaust systems in paint-dip rooms during his study of 106 painters in which the average exposure ranged from 100 to 1,100 ppm.

Atmospheric levels such as those cited above can reflect only the conditions prevailing at the time of an investigation. They do not represent the peak exposures to which workers may be subjected during such incidents as breakdown or leakage of process equipment, transfer operations, etc. In addition, the levels reported during early studies may be inaccurate due to the type of sampling and analytical methods used at that time. These are rarely defined. Also, published reports indicate overexposure almost exclusively and conditions that are within acceptable limits must be deduced by inference.

Environmental Sampling and Analytical Method

Many methods have been used to determine the concentration of toluene vapor in air. Methods of collection have included the use of plastic bags, [61] absorption in scrubbers by nitrating solutions [62,63] or organic solvents, [64,65] and adsorption on silica gel [66] or activated charcoal. [67-69] Analytical methods have included colorimetry, involving nitration followed by reaction with various ketones, [62,63] spectrophotometry, [64,65] direct estimation by means of colorimetric indicator tubes, [70,71] and gas chromatography. [66,67,72]

Of the various methods of collection, adsorption on activated charcoal provides the greatest efficiency and ease of collection. [67,68] The use of absorbing liquids requires additional field sampling equipment and is inconvenient in obtaining personal breathing-zone samples, especially when 2 or more scrubbers must be connected in series to assure a high collection efficiency. [60,67] Activated charcoal is preferable to silica gel because aromatic hydrocarbons, such as toluene, are easily displaced from silica gel by water vapor, resulting in possible losses of the sample when silica gel is used as an adsorbent in humid atmospheres. [66] The design of activated charcoal tubes for the sampling of toluene vapor in industrial atmospheres and the conditions of sampling and desorption have been defined by White et al. [68] They reported average desorption efficiencies of 100% (range, 97-102%) and 95% (range, 93-

96%) for 100 ppm concentrations of toluene sampled alone and in the presence of 6 other organic vapors, respectively.

Gas chromatography offers the greatest specificity and sensitivity of the numerous methods of analysis. [66-68] The various colorimetric methods, and even the direct spectrophotometric methods, are subject to interferences from a wide variety of compounds, and removal of these interferences is tedious and, in many cases, incomplete. [62]

Other sampling and analytical methods can be useful adjuncts to the compliance method outlined in Appendix I, especially for the determination of "exposure to toluene" as originally defined and for special purposes for identification of hazardous conditions. Descriptions of additional methods utilizing detector tubes and portable instruments are given in Appendix II.

Sorbability of Toluene on Charcoal

Concentrations of 200 ppm of toluene were dynamically generated in a NIOSH laboratory to test the sorbability of toluene on charcoal. The following tests were performed:

(a)   Single Section Charcoal Tubes

To obtain an approximate breakthrough value, a charcoal tube containing only one section of charcoal (100 mg) was used to collect toluene from the air. The 200 ppm mixture was drawn through the tube at a rate of 1 liter/minute and a flame ionization detector was placed

downstream of the tube to monitor the toluene vapor coming through the tube. Concentrations coming through the tube were recorded by a strip chart recorder and the point at which the signal noticeably deflected from the initial reading was defined as the point of breakthrough. The average breakthrough volume was 19 liters, obtained from several tubes under these conditions.

(b)   Double Section Charcoal Tubes

These tests were performed using the normal charcoal tubes containing two sections of activated charcoal. Samples were collected at 200 ppm of toluene at a flowrate of 1 liter/minute and for various lengths of time ranging from 10-20 minutes. Breakthrough was defined as the point in sampling at which 0.1 mg of toluene was collected on the 50-mg (backup) section of charcoal. The data points are listed in Table IV-1.

TABLE IV-1

| | | Toluene Concentration | |
Tube No.	Volume sampled (liters)	Front section (mg)	Backup section (mg)
1	17	12.46	0.015
2	17	12.75	0.064
3	18	13.47	0.056
4	18	13.27	0.037
5	19	13.57	0.039
6	19	13.56	0.143
7	20	13.61	0.119
8	20	14.33	0.041

A plot was made of total volume sampled vs weight of toluene on the backup section of charcoal, a parabolic regression analysis was performed, and a curve was plotted. The volume on the curve corresponding to 0.1 mg of toluene on the backup section was selected as the point of breakthrough and was determined to be 19 liters. Therefore, a sample volume of 10 liters (1 liter/minute for 10 minutes) as prescribed in the recommended sampling method provides excellent recovery of the sampled toluene. At this sampled volume of 10 liters, no appreciable amount of toluene will pass to the backup filter.

Accuracy and Precision Data

(a) Analytical Method, Not Including Sampling Error

Eight samples from the breakthrough tests were used to determine the accuracy and precision of the analytical method alone (not including sampling error) as listed in Table IV-2. The 200 ppm toluene concentration was prepared by continuously injecting toluene from a motor-driven syringe into a flowing air stream. The flow rate of the air sampled through the charcoal tube was controlled at 1 liter/minute by a calibrated critical orifice.

The information in Table IV-2 is obtained from a small sampling, but provides a typical example of the accuracy and precision of the method excluding any sampling error.

TABLE IV-2

Tube No.	Total toluene collected (mg)	Volume sampled (liters)	Measured conc. (ppm)
1	12.5	17	195
2	12.8	17	200
3	13.5	18	199
4	13.3	18	196
5	13.6	19	190
6	13.7	19	191
7	13.7	20	182
8	14.4	20	191

Mean $(\bar{X})$ of the 8 measured values = 193.0 ppm

Standard deviation(s) = 5.4 ppm

Accuracy: (1) Systematic error = $\dfrac{200-193}{200} \times 100 = 3.5\%$

(2) Precision (relative standard deviation) =

$$\dfrac{s}{\bar{X}} \times 100 = 2.8\%$$

(b) Analytical Method Using Personal Sampling Pump

(1) No in-line resistance

The accuracy and precision of the overall sampling and analytical method was determined (Table IV-3) on samples using approved coal mine dust personal sampling pumps having no pulsation dampeners and a rotameter calibrated with no in-line resistance. Ten charcoal tube samples were taken using 5 different pumps (2 samples/pump) at different times during the day.

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(A) Sampling procedures

The charcoal tube tips were broken off and the tube was connected to the pump inlet with a three-foot length of Tygon tubing. With pump operation, the rotameter ball was set for the desired flow rate (1 liter/minute), and the toluene-containing air (200 ppm) was sampled for 10 minutes.

TABLE IV-3

Tube No.	Total toluene collected (mg)	Measured conc. (ppm)
1	5.62	149.1
2	5.55	147.2
3	5.03	133.4
4	4.79	127.1
5	5.81	154.1
6	6.35	168.5
7	6.37	168.9
8	6.37	169.1
9	6.05	160.7
10	6.16	163.5

Mean ($\bar{X}$) = 154.2 ppm

Standard Deviation(s) = 150.0 ppm

Accuracy: Systematic error = $\dfrac{200-\bar{X}}{200}$ x 100 = 22.9%

Precision (relative standard deviation) =

$\dfrac{s}{\bar{X}}$ x 100 = 9.7%

Theoretical sampling volume = 10 liters/tube

Generated concentration = 25 ppm

Temperature of sampling = approximately 25 C

Pressure = approximately 745 mm Hg

(2) With In-line Resistance

Ten charcoal tube samples were collected using the same procedure as in (1) above, except that pump calibration was performed with a charcoal tube in line. The results are listed in Table IV-4.

TABLE IV-4

Tube No.	Total toluene collected (mg)	Measured conc. (ppm)
11	7.86	208.7
12	7.88	209.0
13	8.70	231.0
14	8.54	226.9
15	8.01	212.6
16	8.37	222.0
17	7.89	209.3
18	7.79	206.6
19	8.27	219.5
20	7.58	201.1

Mean ($\overline{X}$) = 214.7 ppm

Standard Deviation(s) = 9.7 ppm

Accuracy: (1) Systematic error = $\frac{\overline{X}-200}{200}$ x 100 = 7.4%

(2) Precision (relative standard deviation) =

$\frac{s}{\overline{X}}$ x 100 = 4.5%

The accuracy of the tests with in-line calibration was approximately 16% better than that in (1) above which lacked the in-line calibration.

Biologic Evaluation

The metabolism of toluene involves oxidation and conjugation prior to excretion. Teisinger and Srbova [73] stated that it is oxidized to benzoic acid, the major portion of which is conjugated with glycine in the liver, and excreted mainly as hippuric acid, a water-soluble urinary metabolite. About 20% of the benzoic acid intermediate is conjugated with glucuronic acid with formation of benzoylglucuronic acid.

Ogata et al [74] reporting in 1970 on the excretion of toluene and xylene metabolites showed that during the 18-hour period following the initiation of controlled human exposures to 100 and 200 ppm concentrations the amount of excreted hippuric acid was equivalent to 68% of the toluene absorbed. The excretion of this metabolite, therefore, was relatively rapid.

In their studies, Teisinger and Srbova [73] measured benzoic acid instead of hippuric acid in the urine to take into account the minor portion of the intermediate which is conjugated with glucuronic acid. These investigators reported a mean daily benzoic acid excretion of 0.746 g/day (equivalent to approximately 1 g of hippuric acid). On the basis of their experimental absorption data for

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toluene, they estimated that a worker exposed to 200 ppm of toluene in air excretes approximately 3 to 5 times more benzoic acid than the normal average.

Arato [75] in 1968 reported that although the amount of benzoic acid excreted in the urine of workers exposed to toluene vapor was elevated in all cases, individual variations made it difficult to correlate the urine levels with the air concentrations. Airborne toluene concentrations reportedly varied from 150 mg/cu m to more than 2,000 mg/cu m (40 to 533 ppm). During each workday, the air levels of toluene appeared to undergo wide fluctuations which probably accounts for the difficulty in individual comparisons with environmental levels.

Capellini and Alessio [16] in 1971 reported the urinary excretion of hippuric acid in 17 workers who had been exposed for several years to mean atmospheric concentrations of toluene of 125 ppm (range, 80-160 ppm) measured at the working stations. The control subjects were 19 co-workers who had never been exposed to toluene and whose main meal at the canteen was similar to that of the toluene-exposed workers. The mean urinary hippuric acid value for the controls was 0.95 ±0.33 g/liter (range, 0.55-1.6 g/liter); that measured in samples from the workers was 2.1 ±0.83 g/liter. The difference from the control value was statistically significant (p less than 0.01). All samples were collected at the end of the working day and were analyzed, after solvent extraction, by the ultraviolet

spectrophotometric method of Pagnotto and Lieberman. [60] The urinary results were adjusted to a specific gravity of 1.016. If an adjustment to a specific gravity of 1.024 had been made, the hippuric acid means for the control and for the toluene-exposed (mean, 125 ppm) workers would have been 1.43 and 3.15 g/liter, respectively.

Pagnotto and Lieberman [60] reported in 1967 that their study had shown that exposures of workers to 200 ppm of toluene produced 7 g of hippuric acid/liter of urine as compared with 0.8 g/liter (range, 0.4-1.4 g/liter) for unexposed subjects. The samples were collected at the end of the work shift. Following an extraction with a mixture of isopropyl alcohol and diethyl ether, the hippuric acid was measured at 230 nm in a spectrophotometer. The higher hippuric acid values obtained by these investigators may well have been due to the presence of methylhippuric acid, a metabolite resulting from the mixed exposure of the workers to xylene and toluene in the leather-finishing and rubber-coating plants. Methylhippuric acid also contributes to spectrophotometric absorbance in the 230 nm region.

There is a relatively wide range of hippuric acid excretion levels reported for groups of workers exposed to toluene at given operations. For example, Pagnotto and Lieberman [60] found a range of 2.75 to 6.80 g/liter (mean, 3.66 g/liter) for spreaders in the rubber-coating industry exposed to 34-120 ppm (mean, 73 ppm) of toluene; a 1.024 specific gravity correction was applied in developing these values. In 1969, Ikeda and Ohtsuji, [59] using a specific gravity

correction of 1.016 for groups of Japanese workers in photogravure printing factories, reported hippuric acid excretion values of 8 workers exposed to a 125 ppm average concentration of toluene to range from 2.28 to 3.54 g/liter (mean, 2.84 g/liter).

Ogata et al [76] in 1969 applied paper chromatography to separate hippuric acid from methylhippuric acid and other urinary constituents to improve the specificity of the analysis. With this method and a 1.024 specific gravity correction, these investigators reported hippuric acid excretion levels of 2.55 ±0.55 and 5.99 ±1.20 g/liter of hippuric acid for 23 male volunteers exposed to 100 and 200 ppm toluene, respectively, for 3 hours in the morning and 4 hours after the noon lunch period. The samples were collected at the end of the afternoon exposure period.

The dietary habits of workers provide a potential variable affecting hippuric acid excretion levels. Gerarde [31] has pointed out that hippuric acid is a normal urinary constituent originating in foods containing benzoic acid or benzoates.

It is on the basis of these studies that a recommended level of 5 g/liter of hippuric acid in urine has been selected to correlate with the time-weighted average of 200 ppm of toluene vapor. This level of urinary hippuric acid represents an unacceptable absorption of toluene posing a possible risk of toluene intoxication. The measurement of urinary hippuric acid is more of a diagnostic practice than one of compliance. It is not a mandatory procedure but is left

to the discretion of the medical supervisor to be included in the medical program. Biologic monitoring, therefore, provides a valuable measurement technique to verify toluene exposure in the individual worker.

Ellman et al [77] have reviewed the early methods of hippuric acid analysis. The methods involved crystallization, ether extraction, and determination of hippuric acid by weighing, titration, or Kjeldahl analysis. The methods are seldom used today because they are tedious and do not always produce quantitative results. More acceptable procedures have been based on colorimetry, [59,60,74,76,78,79] fluorimetry, [77] and ultraviolet spectrophotometry. [80,81] Improved specificity has been achieved with some of the methods by preliminary sample treatment with ion-exchange resin, [81] paper chromatography, [59,76,78] or alcohol-ether extraction. [60]

Colorimetric methods are used most frequently for the determination of hippuric acid in urine. The method used by Pagnotto and Lieberman [60] successfully detected urinary hippuric acid in unexposed and toluene exposed workers. The average values were reported to be 0.8 g/liter for unexposed subjects and 7.0 g/liter for workers exposed to 200 ppm of toluene (adjusted to a specific gravity of 1.024). However, their spectrophotometric method was not specific for hippuric acid but measured hippuric, methylhippuric, and uric acids at the same wavelength. Other investigators [59,76] have

developed methods which are more specific for hippuric acid, and thus, urine levels reported for the same toluene concentration are slightly lower than those reported by Pagnotto and Lieberman. Ikeda and Ohtsuji, [59] using paper chromatography, reported 3.5 g/liter in workers exposed to 200 ppm of toluene. Their value was adjusted to a specific gravity of 1.016; if adjusted to 1.024, the value would have been 5.3 g/liter. Ogata et al, [76] in order to improve specificity, formed an azlactone derivative of the urinary hippuric acid. This improved method is particularly advantageous in monitoring workers exposed to mixed vapors of toluene and m- or p-xylene since it provides for the separation of the respective xylene metabolites, namely m- or p-methylhippuric acids.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1943, the U.S. Public Health Service [82] published a table of toxic limits in which toluene was given a value of 200 ppm based on the 1942 reports of von Oettingen et al [21] and Greenburg et al. [37]

The Z.37 Committee of the American Standards Association, now known as the American National Standards Institute (ANSI), in 1943, published a standard of 200 ppm for an 8-hour daily exposure to toluene based likewise on the reports of von Oettingen and Greenburg. ANSI has periodically reaffirmed this standard and in 1969, a time-weighted average of 200 ppm was approved. [83] A ceiling of 300 ppm was also recommended along with an acceptable maximum excursion of 500 ppm for a duration of not more than 10 minutes, provided such an exposure is encountered not more than once a day. The acceptable excursion level and duration were based purely on judgment by the Committee (WA Cook, written communication, 1973). Examination of the literature by NIOSH has failed to find data to support such an excursion above a ceiling or any other level relating concentration and time.

In 1947, the American Conference of Governmental Industrial Hygienists (ACGIH) [84] established a Threshold Limit Value (TLV) for toluene of 200 ppm, based on the report of Wilson [23] that physical findings among workers exposed to toluene concentrations below 200 ppm

were essentially negative. In 1971, the ACGIH [85] lowered the threshold limit for toluene to 100 ppm on the basis of irritative effects on the eyes, mucous membranes, and upper respiratory tract of individual subjects exposed variously to 200 to 500 ppm.

In 1957, the Hygienic Guides Committee of the American Industrial Hygiene Association [86] recommended a Maximum Atmospheric Concentration (MAC) of 200 ppm of toluene vapor by volume for 8 hours. This MAC was based on human experience in industry and toxicologic observations in animals.

The present Federal Standard for toluene is an 8-hour time-weighted average of 200 ppm with a ceiling concentration of 300 ppm not to be exceeded during any 8-hour shift. In addition, a maximum peak of 500 ppm for a maximum duration of 10 minutes is acceptable during the 8-hour work shift (29 CFR Part 1910.93 published in the Federal Register, volume 37, page 22139, dated October 18, 1972). This Federal Standard is based on ANSI Z37.12-1967. [83]

Basis for Recommended Environmental Standard

Von Oettingen et al [21,22] have provided the most complete description of the effects of pure toluene on the central nervous system. In this controlled series of exposures of 3 human subjects, no distinct symptoms or after-effects were reported for the 50- and 100-ppm exposures other than drowsiness and mild-to-moderate fatigue as well as a very mild headache by one of the subjects toward the end

of the 8-hour exposure. Moderate tiredness was experienced by these same subjects toward the end of an 8-hour exposure to a zero concentration of toluene in the exposure chamber probably because of a lack of physical exercise, unfavorable illumination, and monotonous noise (fans) where they were occupied during all experimental exposures with their usual routine work to minimize monotony and lack of occupation. At a 200-ppm exposure level, however, two of the subjects experienced muscular weakness, impaired coordination, confusion, and paresthesias of the skin. At the higher exposure levels the symptoms became more pronounced. At 400 ppm all 3 subjects showed signs of mental confusion, fatigue, exhilaration, headache, nausea, and dizziness at the end of 3 hours and, at the end of 8 hours, they showed marked incoordination and a staggering gait. Finally, at 800 ppm all subjects were very confused and showed a lack of self-control and a staggering gait at the end of three hours. Observed variations in the leukocyte count, pulse rate, diastolic blood pressure, pulse pressure, respiratory rate, and minute volume to exposures from 50 to 800 ppm were within control limits.

Carpenter et al [24] reported transitory mild throat and eye irritation and slight exhilaration experienced by 2 male subjects given one-time exposures to 200 ppm of toluene for 7 or 8-hour periods. This was the lowest concentration which was studied. The possibility of benzene contamination was not mentioned in the report.

More recently, Ogata et al [74] in 1970 reported that Japanese subjects given single exposures to 200 ppm of toluene for a period of 7 hours showed a prolongation of eye-to-hand reaction time, a decrease in pulse rate, and a statistically insignificant decrease in systolic blood pressure. No physiological changes were reported at exposures to 100 ppm. They did not consider that 200 ppm of toluene was safe on the basis of their observations.

Capellini and Alessio [16] in 1971 reported that 17 workers who had been exposed for "several" years to mean atmospheric concentrations of toluene of 125 ppm (range 80-160 ppm) and one worker who had mean exposures of 250 ppm (range 210-300 ppm) showed no changes in the blood picture which included Hgb values, RBC, WBC, and platelet counts, or changes in liver function as compared with 19 control subjects. Although no blood abnormalities were detected in any case, the worker whose job activity entailed mean toluene exposures of 250 ppm had irritation of the conjunctiva and central nervous system effects described as a feeling of stupor during work, followed by insomnia and nervousness. Although not reported, the toluene is assumed to have been relatively free of benzene contamination since members of the Italian clinic from which this report originated have published extensively in recent years on the toxicity of benzene in industrial workers.

In summary, changes in muscular coordination, reaction time, and production of mental confusion and irritation of mucous membranes have

been observed for toluene exposures to 200 ppm. These adverse effects have not been reported for toluene exposures of 100 ppm or less in industrial workers or experimental subjects. Although only 3 subjects were employed in the study of von Oettingen et al, [21,22] the findings reported by Carpenter et al, [24] Ogata et al, [74] and Capellini and Alessio [16] help to corroborate the report of von Oettingen et al as being valid for setting a standard. It is recommended, therefore, that the 8-hour time-weighted exposure to toluene be established at 100 ppm.

Of further importance is the current evidence from studies using purified toluene that the chemical lacks toxic effects on the blood or on blood-forming organs. [15,17,33,38,46,47,49] The myelotoxic effects previously attributed to toluene from early studies are presently judged by updated investigations to be the result of concurrent exposure to benzene present as a contaminant. Evidence in the literature [21,22,24,74] that the fatigue, dizziness, exhilaration, and mental confusion resulting from exposures of subjects to concentrations of toluene above 200 ppm for several hours, argues for a ceiling limit of 200 ppm as part of the environmental standard. A ceiling of 200 ppm will limit the range of exposure in the work environment in a manner consistent with the 8-hour time-weighted average recommendation of 100 ppm so as to preclude acute narcotic effects from exposure to toluene.

Liver injury has been reported after continued exposure to apparently high toluene concentrations [36] with resultant recovery following treatment. The findings of liver enlargement in painters reported by Greenburg et al [37] in 1942 indicated toluene exposures up to 1,100 ppm but no correlations could be made between the hepatomegaly and the concentrations of toluene which were encountered. Investigations of the literature by NIOSH have failed to show any reports of permanent liver damage as a result of exposure to toluene even in the few reports where liver enlargement has been mentioned. Apparently any alterations in the liver, even to high toluene concentrations, are reversible. Workers exposed for many years to toluene concentrations in the range of 80 to 300 ppm have failed to show any clinical or laboratory evidence of altered liver function [16]; therefore, it is considered that the recommended standard will prevent adverse effects of toluene on the liver.

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