

Kidney disorders and hematotoxicity from organic solvent exposure

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LAUWERYS R, BERNARD A, VIAU C, BUCHET J-P. Kidney disorders and hematotoxicity from organic solvent exposure. *Scand J Work Environ Health* 11 (1985): suppl 1, 83–90. Short-term exposure to certain solvents, such as several halogenated hydrocarbons, petroleum distillates, ethylene glycol, ethylene glycol ethers, and diethylene glycol, may cause renal tubular necrosis. Tubular lesions with metabolic acidosis have been reported in addicts inhaling solvent vapor (eg, toluene). A Goodpasture's syndrome may be induced by acute or subacute exposure to solvents, but its incidence is rare. No adequate proof is yet available that repeated exposure to nonsubstituted organic solvents may lead to the development of different types of chronic glomerulonephritis, but the available epidemiologic data are suggestive of the existence of such an association. Only a few solvents have been reported to act on the hematopoietic system of humans. The hematotoxicity (aplastic anemia, leukemia) of benzene is well established. Some ethylene glycol ethers are also toxic to bone marrow.

Key terms: bone marrow toxicity, humans, kidney toxicity, solvents.

This paper has been restricted to a review of the available data regarding the effects of solvents on the kidney and the hematopoietic system of humans.

Renal effects of solvents in humans

Several solvents are nephrotoxic. Depending upon kind, concentration, and duration of exposure, the renal effects may be acute or chronic and involve the tubules or the glomeruli.

Renal effects usually associated with acute or subacute exposure to solvents

Short-term exposure to certain solvents, such as various halogenated hydrocarbons, petroleum distillates, ethylene glycol, ethylene glycol ethers, diethylene glycol, and dioxane, may cause tubular necrosis, a life-threatening situation characterized by oliguria and azotemia (22, 37, 41, 47). The tubular lesion due to acute solvent exposure occurs promptly after exposure (the latency period not usually exceeding a few days), and therefore the establishment of a relationship between exposure and effect does not create much of a problem.

The morphological changes are confined to the tubules; the glomeruli are intact. The tubular epithelium undergoes changes ranging from swelling, ballooning, and hydropic changes to necrosis. The tubular lumen

may contain desquamated cells, pigmented casts, or eosinophilic amorphous granular material (16). The presence of oxalate crystals in the tubular lumen is typical of glycol poisoning.

The occurrence of tubular lesions leads to a diffuse, homogeneous reduction of renal cortical perfusion (26). This vasomotor reaction may be exacerbated by a passive back flow of glomerular filtrate across disrupted tubular epithelium which, in association with tubular lumen obstruction by cell debris and increased renin released from juxtaglomerular cells, may account for the sustained oliguria and azotemia.

The majority of the renal tubular toxins are not directly active, but must first be activated in the organism.

Different mechanisms of action are probably responsible for the initial events leading to renal tubular cell damage. Unfortunately, for the majority of solvents, the early critical effects are still speculative. Contrary to what was believed in the past, the acute renal toxicity of ethylene glycol and its ether derivatives does not depend solely on the precipitation of oxalate crystals in the tubular lumen. Other toxic mechanisms are likely to be involved. It has been suggested that the critical toxic events after the activation of carbon tetrachloride (CCl_4) into the trichloromethyl radical ($\cdot\text{CCl}_3$) and its covalent binding to microsomal lipids is a disturbance of intracellular calcium homeostasis (51).

Before the advent of peritoneal dialysis and hemodialysis, chemically-induced massive tubular necrosis was usually fatal. Now the outcome is more favorable. It takes about three weeks for the tubular epithelium to regenerate. Recovery may be complete, but, depending on the severity of the intoxication and the previous status of renal function, some degree of renal in-

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sufficiency may persist. Depending on the solvent involved, organs other than the kidney may also be damaged, eg, the central nervous system after acute exposure to ethylene glycolmethyl ether and the liver following acute exposure to some aliphatic hydrocarbons (eg, carbon tetrachloride).

An association between acute or subacute heavy exposure to solvents and Goodpasture's syndrome has been frequently reported (6, 9, 16, 30, 31, 40). It has been suggested however that the syndrome might also occur after moderate or even low exposure to hydrocarbon solvents (eg, methylene chloride and 1,1,1-trichloroethane).

The diagnosis of Goodpasture's syndrome is usually based on the triad of glomerulonephritis, intra-alveolar pulmonary hemorrhage, and the demonstration of antiglomerular basement membrane antibody (7). The classical syndrome with rapid evolution and poor prognosis is fortunately rare. Since the development of sensitive tests for detecting antiglomerular basement membrane antibody, milder forms with minimal renal involvement are more frequently recognized. Lung symptoms may not necessarily be always present (29). Sometimes the clinical syndrome is that of a proliferative glomerulonephritis of slow progression (6, 17). The mechanism of the lesion is believed to be the following: the inhalation of solvent vapor induces chemical damage to the alveolar basement membrane leading to the production of antialveolar basement membrane antibodies which cross-react with the glomerular basement membrane and initiate the renal glomerular disease (9). The rare occurrence of Goodpasture's syndrome after solvent exposure suggests that some other facilitating factors are involved in the disease. Rees et al (52) found, for example, that there is a significant association between the presence of HLA DRW₂ (human leukocyte antigen DRW₂) and the ability to synthesize antibodies directed against the glomerular basement membrane.

Renal effects usually associated with chronic exposure to solvents

Case reports have been published suggesting that the repeated inhalation of toluene-containing solvents (eg, by glue sniffers) may lead to proximal and distal renal tubulopathy with aminoaciduria, glucosuria, hyperchloremic acidosis, hypokalemia, hypocalcemia, hypophosphatemia, and hypouricemia (20, 38, 42, 57, 58, 62, 63). These lesions might be reversible with abstinence from glue sniffing.

Several case reports have also been published suggesting an association between solvent exposure (gasoline, gasoline-based paint spray, jet fuel, mineral turpentine) and various forms of glomerulonephritis. The majority of these cases has been summarized by Churchill et al (10). As stated by these authors, case reports do not prove the existence of a causal relationship. They are only suggestive of an association,

which must be evaluated through well-designed epidemiologic studies.

The results of the three types of epidemiologic approaches [cross-sectional surveys of workers chronically exposed to a solvent or solvents, case-referent (case-control) studies, cohort mortality studies] which have been used to investigate this problem can be summarized as follows.

Cross-sectional studies. A few cross-sectional epidemiologic studies attempting to evaluate the possible toxic effects of chronic exposure to organic solvents on the kidneys of workers have been reported.

Swedish studies: Askergrén (3) summarized the results of his studies (2, 5) with two age-matched groups of male subjects. The reference group consisted of 48 employees and manual workers (mean age 47.6 years, range 20–64 years) without a history of exposure to organic solvents. The exposed group comprised 134 subjects (mean age 43.2 years, range 20–64 years) with occupational exposure either to styrene (N = 52, plastic boat manufacturing) or to toluene (N = 42, photogravure printing plants) or to solvent mixtures containing mainly toluene and xylene (N = 40, paint plants). There were no differences between the referents and the exposed subjects with respect to case histories of previous renal and urinary tract diseases. No glomerulonephritis was recorded. The styrene concentration in the ambient air intermittently increased up to 925 mg/m³ for certain jobs and varied between 100 and 300 mg/m³ for others; the background levels were 20–100 mg/m³. Toluene exposure amounted to 300–400 mg/m³ for the printers, and in the paint plants the time-weighted average (TWA) concentrations (1 d) varied between 10 and 50 % of the Swedish hygienic limit values, which are 300 and 350 mg/m³ for toluene and xylene, respectively.

The renal function of the referents and the exposed subjects was evaluated for measurements of the following parameters: albuminuria, β_2 -microglobulinuria, urinary concentrating ability, urinary excretion of cells, and the clearance of 51-chromium-ethylene diamine tetraacetic acid. There was no difference between the referents and the exposed groups as to β_2 -microglobulinuria, concentrating ability, or glomerular filtration rate. The exposed subjects exhibited, on the average, a significantly greater degree of albuminuria (the greatest being found in the styrene-exposed workers) and excreted more erythrocytes and white/tubular epithelial cells in urine than the referents. The mean value for the referents and exposed subjects was 3.7 (range 0–21) mg/l versus 15.8 (range 0–440) mg/l for albuminuria, and there were statistically significant differences in the number of referents and exposed subjects with either albuminuria above 10 mg/l (3 vs 26) or below 1 mg/l (10 vs 7). The electrophoretic pattern of the urinary proteins indicated a glomerular type of proteinuria in six of the exposed subjects by the

presence of immunoglobulins and/or transferrin. Electrophoresis did not reveal any such proteins in the urine of the referents. Askergrén (3) concluded:

The finding of an increased excretion of high molecular weight proteins suggests an enhanced permeability of the glomerular basement membrane. The cause of increased cell excretion is not known. The changes in the kidneys were not advanced enough to show any impairment in GFR [glomerular filtration rate] or in proximal or distal tubular function [p 169].

At the XXI International Congress on Occupational Health in Dublin (September 1984), Askergrén (4) reported the results of a survey of 275 construction workers. They confirm his previous results, i.e., in workers exposed to solvents, the urinary excretion of cells was elevated. The pattern of the protein excretion was mainly of the glomerular type.

Italian studies: Mutti et al (39) reported a cross-sectional study on workers exposed to aliphatic and alicyclic C₅–C₇ hydrocarbon mixtures (mostly n-hexane and cyclohexane) in shoe factories. Serum creatinine and the urinary excretion of albumin, lysozyme, β -glucuronidase activity, and total protein were investigated in 182 currently exposed workers (59 males and 123 females, overall mean age 39.4 years), as well as in 30 workers with past exposure (10 males and 20 females, overall mean age 41.6 years) and 80 referents (30 males and 50 females, overall mean age 37.9 years). The present or past exposure period varied, on the average, from 8.4 to 10.2 years, and in most cases the ambient air concentrations of organic solvents at each workplace exceeded the threshold limit value recommended for the mixture by the American Conference of Governmental Industrial Hygienists (ACGIH). In the group of currently exposed workers significantly higher proteinuria was found as compared to that in the referents or in the group of previously exposed workers. In seven presently exposed workers, proteinuria slightly exceeded the referents' mean plus two standard deviations. None of the exworkers had such a degree of proteinuria. None of the workers had abnormal albuminuria or serum creatinine. In four of the seven presently exposed workers with proteinuria slightly exceeding the referents', a slight increase in lysozymuria was found, and the activity of urinary β -glucuronidase was elevated in two of them. Moreover, the mean values of the urinary excretion of these two enzymes were significantly higher in these seven workers than in age- and sex-matched referents. These findings suggest that a mild and presumably reversible tubular dysfunction, but no glomerular impairment, may occur in workers occupationally exposed to C₅–C₇ hydrocarbon mixtures.

Franchini et al (21) studied 438 workers exposed to organic solvents in 11 factories and 29 dry-cleaning shops, including also the 212 shoemakers of the aforementioned study of Mutti et al (39). The other 226 workers were distributed into three groups, and

their exposure was characterized by means of urinary metabolites as follows: (i) dry cleaners (N = 57, mostly female; average age and duration of exposure 43.0 and 13.9 years, respectively) exposed to perchloroethylene (estimated TWA concentration about 10 ppm); (ii) painters (N = 118, mostly male; average age and duration of exposure 40.2 and 9.1 years, respectively) exposed to toluene and xylene (estimated toluene TWA concentration about 25 ppm); and (iii) laminators of glass fibers (N = 51, mostly male; average age and duration of exposure 35.9 and 6.4 years, respectively) exposed to styrene (estimated TWA concentration about 50 ppm). The mean albuminuria values did not differ between the reference and exposed groups. However, compared to the values of the reference groups, significantly higher mean values were found for proteinuria in shoemakers (C₅–C₇ alkanes) and laminators (styrene), for urinary β -glucuronidase activity in dry cleaners (perchloroethylene) and painters (toluene and xylene), and for lysozymuria in dry cleaners and laminators. Those workers with proteinuria higher than the upper normal limit also showed an increased urinary excretion of lysozyme and/or β -glucuronidase activities, but not of albumin. In summary, at the prevailing exposure levels, renal dysfunction seems to be very mild and tubular in nature, rather than glomerular.

Although Askergrén (3, 4) and Franchini et al (21) have found some renal effects in workers exposed to solvents, their results do not suggest the same site of action. It should, however, be pointed out that Askergrén (3, 4) mainly studied workers exposed to aromatic hydrocarbons (toluene, xylene, styrene), whereas in the study of Franchini et al (21) the workers with the heaviest exposure to solvents were mainly exposed to C₅–C₇ aliphatic or alicyclic hydrocarbons.

French study: At the XXI International Congress on Occupational Health in Dublin (September 1984) Brochard et al (8) reported that among 20 000 workers routinely examined by occupational health physicians the prevalence of elevated proteinuria was significantly higher for those exposed to solvents for at least one year (0.96 %) than for the unexposed subjects (0.52 %).

Belgian study: We have examined 180 workers exposed to various solvents and 170 sex- and age-matched referents (unpublished results). The exposed workers were subdivided as follows:

Group 1: 32 males exposed to n-hexane in a rubber tire factory; average age and duration of exposure 29.9 and 6.8 years, respectively; estimated TWA concentration 12 (range 2.6–38) ppm.

Group 2: 33 males exposed to white spirit in the metallurgical industry; average age and duration of exposure 42.2 and 8.5 years, respectively; estimated TWA concentration 15.6 (range 1.5–66.9) ppm.

Group 3: 23 males exposed to styrene in a polyester producing factory; average age and duration of exposure 31.8 and 1.6 years, respectively; estimated TWA concentration 20 (range 8–44) ppm.

Group 4: 24 females exposed to tetrachloroethylene in dry-cleaning shops; average age and duration of exposure 32.9 and 7 years, respectively; estimated TWA concentration 20.8 (range 8.9–37.5) ppm.

Group 5: 23 males exposed to methyl ethyl ketone during steel plate painting; average age and duration of exposure 29.2 and 4 years, respectively; estimated TWA concentration 33.9 (range 3.1–215.6) ppm.

Group 6: 43 males exposed to a mixture of solvents (mainly white spirit and toluene) in a car painting factory; average age and duration of exposure 36 and 6 years, respectively; estimated TWA concentration; white spirit 7.3 (range 3–14.3) ppm, toluene 2.1 (range 0.6–4.5) ppm.

Exposure to each solvent was moderate since all the mean airborne concentrations were well below the current ACGIH threshold limit values. Furthermore the average duration of exposure was less than 10 years. The mean concentrations of urinary β_2 -microglobulin, retinol-binding protein, and albumin and the prevalence of increased values of the same parameters were not significantly different between the referents and the corresponding exposed groups. The only statistically significant difference was a slight shift of the cumulative frequency distribution of the urinary albumin concentration towards higher values in the styrene group in comparison with the values of the reference group. This result is in agreement with the observations of Askergrén (3).

*Case-referent studies.*² Seven case-referent studies have been published. Tables 1 and 2, adapted from Churchill et al (10) and from Phillips (46), summarize the main characteristics and the results of these studies.

Zimmerman et al (64) interviewed 63 adult patients with advanced renal failure to evaluate their exposure to chronically contacted or inhaled toxic substances. The interview was not blinded. The grading of exposure revealed that patients with primary proliferative glomerulonephritis in biopsies and patients with a

clinical presentation consistent with glomerulonephritis had significantly greater exposure to hydrocarbon solvents than patients with a variety of other renal diseases.

Laguerre et al (31) evaluated the exposure to organic solvents in 247 cases of primary chronic glomerulonephritis. Their exposure was compared with that of a reference population of 124 patients suffering from hypertension, urinary infection, or kidney stones. The interview was probably not blinded. Exposure to inhaled toxic substances was found for 142 patients (57.5 %) and 27 referents (20.9 %). The degree of exposure was significantly higher for the patients than for the referents. When the patients were classified according to histological findings, the frequency of exposure was similar in all the groups. Industrial substances (hydrocarbon solvents, chiefly fuels and paints) were involved in most cases.

Ravnskov (48) asked 15 patients with evidence of acute poststreptococcal glomerulonephritis about their contact with vapors of organic solvents. Fifteen age- and sex-matched patients who had been infected with nephritogenic streptococci but who did not develop glomerulonephritis served as the referents. Ten of the former group had been exposed to solvents before the onset of glomerulonephritis but none of the latter group.

Another case-referent study performed by Ravnskov et al (49) points in the same direction. Fifty Swedish patients with glomerulonephritis in biopsies and 100 sex- and age-matched referents (of which 50 were patients with nonglomerular renal disease and 50 were suffering from acute appendicitis) were asked by questionnaire and a telephone interview whether they had been exposed to organic solvents. The interview was blinded. Fifty percent of the patients with glomerulonephritis, but only 20 % of the referents, reported more than slight exposure. The risk ratio was 3.9.

For 37 patients with biopsy-proved or suspected glomerulonephritis, Finn et al (19) found a relative risk of exposure to solvents of 4.4 in a comparison with hospitalized patients with other types of disease.

van der Laan (60) compared the organic solvent exposure of 50 patients with histologically confirmed chronic glomerulonephritis and 50 reference patients with a variety of internal diseases. No difference in exposure between the cases and referents was found. The interview was not blinded, and it was not stated whether the patients whose glomerulonephritis was part of a systemic disease were excluded from the study.

To prevent the possible influence of recall bias, a disadvantage inherent to case-referent studies, Ravnskov et al (50) compared the distribution of occupations among 124 adult patients with nonsystemic glomerulonephritis with that among the general population of the area served by the hospital. They took the occupations which patients had given in a public census before they knew about the suspected

² Note added in proofs: Since the completion of this review, the result of another case-referent study designed to assess the association between chronic glomerulonephritis and solvent exposure has been published. Bell et al compared the organic solvent exposure score of 50 patients with biopsy-proved primary proliferative glomerulonephritis with the score obtained for a group of 100 well-matched referents. Significantly higher exposure scores were observed in the glomerulonephritis group (13 186 versus 3 030, $p < 0.01$). [Bell GM, Gordon ACH, Lee P, Doig A, MacDonald MK, Thomson D, Anderton JL, Robson JS. Proliferative glomerulonephritis and exposure to organic solvents. *Nephron* 40 (1985) 161–165].

relation between hydrocarbon exposure and glomerulonephritis. Occupations assumed to be linked with exposure to organic solvents or fuels were more common among the patients than among the general population.

Despite the methodological deficiencies of several case-referent studies, we are inclined to believe that the consistency between several studies strongly suggests the existence of an association between exposure to solvents and the development of glomerulonephritis.

Cohort mortality studies. Two cohort mortality studies of workers exposed to hydrocarbons [one carried out in oil refineries (54) and the other in the paint industry (36)] did not find an increased standardized mortality ratio for chronic nephritis or urogenital tract diseases, although in one refinery in the United Kingdom the observed ($N = 6$) number of deaths from chronic nephritis was three times the expected number ($N = 2.09$). No conclusion can be drawn from these studies. It is likely that only chronic glomerulonephritis progressing to end-stage renal disease has been indicated as the underlying cause of death on the death certificate, and, furthermore, if chronic glomerulonephritis is induced by a few solvents only, large scale mortality studies on workers exposed to several groups of solvents may not necessarily detect this effect.

Chronic exposure to gasoline has been linked with the development of renal cancer in male, but not in female, rats. Six epidemiologic studies have examined the question of possible excess renal cancer among refinery workers. Their results have been summarized by Savitz & Moure (55). In one of these studies a statistically significant increase in the relative risk (2.14) of renal cancer was found among workers exposed for

more than 20 years. Another study found a non-statistically significant increase in the relative risk (2.05) of the more highly exposed subset of workers. The other studies did not provide data supporting an excess risk of kidney cancer.

Conclusion. Although there is not yet adequate proof that repeated exposure to nonsubstituted organic solvents may lead to the development of different histological types of chronic glomerulonephritis, the available epidemiologic data (case-referent studies and cross-sectional studies) are suggestive of the existence of such an association. However, the risk, if any, does not seem very high. Nevertheless, this possibility justifies the removal of workers with signs of renal insufficiency from solvent exposure and regular screening of workers exposed to solvents for an increased urinary excretion of proteins.

Effects of solvents on the hematopoietic system

Only a few solvents have been reported to act on the hematopoietic system in humans, ie, benzene, styrene, and some glycol ethers.

Benzene

The recognition of the important hematotoxicity of benzene has led to the enactment of regulations restricting its use in many countries. Currently benzene is mainly used as a raw material for organic synthesis. It is also a constituent of gasoline.

Benzene can cause aplastic anemia and leukemia. A detailed bibliography on benzene toxicity can be

Table 1. Characteristics of the case-referent studies of renal disease and hydrocarbon exposure [adapted from Churchill et al (10)].

Year	Authors	Reference group	Interviews	Recal bias
1975	Zimmerman et al (64)	Confounder: sex, employability	Not blinded	Probably present
1977	Laguer et al (31)	Confounder: employability	Not blinded	Probably present
1978	Ravnskov (48)	Acceptable	Not blinded	Probably present
1979	Ravnskov et al (49)	Acceptable	Blinded	Probably present
1980	Finn et al (19)	Confounder: employability	?	Probably present
1980	van der Laan (60)	Acceptable	Not blinded	?
1983	Ravnskov et al (50)	Acceptable (general population)	Blinded	Absent

Table 2. Results of seven case-referent studies of renal disease and hydrocarbon exposure [adapted from Philips (46)]. (PGN = primary glomerulonephritis).

Year	Authors	Number of cases	Number of controls	Relative risk for solvent exposure
1975	Zimmerman et al (64)	28 (PGN)	35	> +
1977	Laguer et al (31)	247 (PGN)	124	4.8
1978	Ravnskov (48)	15	15	> +
1979	Ravnskov et al (49)	50	100	3.9
1980	Finn et al (19)	37	105	4.4
1980	van der Laan (60)	50	50	1.1
1983	Ravnskov et al (50)	124	— (general population)	> +

found in reviews by Goldstein (24), Snyder & Kocsis (56), and Van Raalte & Grasso (61).

The hematotoxicity of benzene is expressed primarily as bone marrow destruction. Various biological changes have been reported as early signs of benzene hematotoxicity, ie, macrocytosis, shortened red cell survival, abnormal morphology and function of granulocytes (including a decrease in phagocytic ability), a lowered leukocyte alkaline phosphatase activity, altered osmotic fragility, changes in platelet morphology and function, and increased levels of hemoglobin F. At a more advanced stage, benzene toxicity can manifest itself as a paradoxical alteration of the blood picture. Anemia and polycythemia, leucopenia, and leucocytosis have all been reported in exposed workers. With continued exposure, however, the trend is toward decreased levels of circulating erythrocytes, leukocytes, and thrombocytes or any combination of these effects. Early removal of the worker from benzene exposure may still result in complete recovery. In severe cases, however, patients suffer from pancytopenia. The reticulocyte count is low for the degree of anemia, and this phenomenon highlights the defect as a hypoproliferative state. The decrease in the concentration of neutrophils is associated with a reciprocal relative increase in the concentration of lymphocytes. The platelet count is also markedly decreased. Marrow aspirate reveals a hypocellular specimen with a relative predominance of lymphocytes. Fat may have replaced normal functional marrow tissue. The lesion seems to be due to injury of multipotential stem cells (18). Benzene-induced aplastic anemia is a potentially fatal disorder which, in its severe form, has more than a 50 % mortality rate. In current occupational situations, such lesions are rare however.

Benzene is also a leukemogenic agent. This effect of benzene is reviewed in another paper and will only be briefly discussed here. The first clinical observation of benzene-induced leukemia was made by Delore & Borgomano in 1928 (12). Since then, many case reports and several epidemiologic studies have clearly demonstrated that benzene can induce acute myelogenous leukemia and its variants (acute myelomonocytic leukemia, acute promyelocytic leukemia, erythroleukemia).

According to Goldstein (24), there are strong, although still inconclusive, arguments suggesting an association between benzene exposure and chronic myelogenous leukemia, chronic lymphocytic leukemia, Hodgkin's disease, and paroxysmal nocturnal hemoglobinuria. Other hematologic disorders have been linked with benzene exposure (acute lymphoblastic leukemia, myelofibrosis and myeloid metaplasia, lymphoma, thrombocythemia), but the relationship remains to be confirmed.

None of the epidemiologic studies performed so far permit the identification of a clear-cut dose-response relationship between benzene exposure and the risk of leukemia. The conclusion of Infante et al (27) and

Rinsky et al (53) that exposure as low as 10 ppm could still be associated with an increased risk of leukemia deaths has been challenged (61). It is still debatable whether acute myelogenous leukemia occurs only in patients who have developed some degree of cytopenia or whether, in some individuals, it may be the first manifestation of overexposure to benzene. If the first hypothesis is correct, the prevention of pancytopenia would also prevent the development of leukemia. This is an important issue because it is generally accepted that the current TWA concentration of 10 ppm is sufficient to protect against symptomatic pancytopenic effects. It is likely that a satisfactory answer to this question will not be provided until the mechanism of benzene-induced aplastic anemia and leukemia has been unraveled.

Chromosome aberrations have been found in lymphocytes and in bone marrow cells of patients with benzene hemopathy (1). Several authors have also reported an increased rate of chromosome aberrations (mainly gaps and breaks) in workers occupationally exposed to benzene. These chromosome abnormalities may persist for many years, even after the cessation of exposure. No dose-effect relationship has so far been demonstrated for benzene-induced chromosome aberrations, and the implication of this finding for the occurrence of benzene leukemia is still not clear (59).

Although the susceptibility to benzene exhibits great individual variability, there is no good epidemiologic evidence suggesting that one population group (eg, women, pregnant women, young age group) is more at risk than another. Long delays have sometimes been noted between the cessation of benzene exposure and the manifestation or discovery of hematologic disorders (24). It is thus possible that a delayed onset of clinical manifestations may lead to a lack of recognition of previous benzene exposure by the patients or physicians.

It is generally accepted that benzene requires metabolic activation to exert its effects on the bone marrow, but the active metabolite(s) has (have) not yet been clearly identified. Kinoshita et al (28) have obtained evidence that benzene oxide, the predominant intermediate in the metabolic conversion of benzene to phenol, can damage deoxyribonucleic acid. It has also been suggested that the binding of hydroquinone, a metabolite of benzene, to tubulin prevents its polymerization, which may lead to various chromosome abnormalities (61).

Styrene

Some authors have reported an increased prevalence of leukopenia, sometimes in association with other hematologic changes (eg, slight anemia), among workers exposed to styrene. On the contrary, other authors have not found any hematologic disorder in men chronically exposed to styrene. [For a literature review, see the report of Oltramare et al (44).] Ex-

perimental data do not suggest that styrene is a potent hematologic toxin.

A nonstatistically significant excess of tumors of the hematopoietic system has been reported for workers occupied in the production of the synthetic rubber styrene-butadiene (15, 32). Since both styrene and butadiene have been found to be mutagenic (13), the role of styrene, if any, is uncertain. Furthermore other chemicals are also used for the production of styrene-butadiene rubber.

Glycol ethers

Clinical experience and experimental studies have demonstrated that some ethylene glycol ethers (ethylene glycol monomethyl ether, ethylene glycol monoethyl ether) possess bone marrow toxicity (25, 33, 43, 45). The toxicity of ethylene glycol monomethyl ether results from its activation into methoxyacetic acid in the organism (34, 35).

Recently, Cullen et al (11) examined seven printers exposed to a mixture of ethylene glycol monoethyl ether and dipropylene glycol monomethyl ether. They had a normal complete blood count, but bone marrow specimens showed clear patterns of injury in three, while the others had nonspecific signs of marrow effect. In view of the experimental data, it is likely that the bone marrow injury resulted from the exposure to ethylene glycol monoethyl ether.

Overexposure to ethylene glycol ethers may result not only from the inhalation of vapors, but also from direct skin contact (43).

In animals, 2-n-butoxyethanol, 2-t-butoxyethanol, and 2-isopropoxyethanol exert hemolytic activity (14, 23).

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