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Biochemical Research Laboratory
THE DOW CHEMICAL COMPANY

Subject A STUDY OF THE TOXICITY OF BENZENE--LITERATURE SURVEY

File T14-1m4 -1
Chg. 1210
Rec'd 1-19-40
Fin'd. 1-19-40
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To File Report Check OO Grieb 1-24-40 Rept. By H. E. Spencer

Single Exposures

Henderson and Haggard (Noxious Gases, 1927 p. 164) give the following data (cited from Technical Paper 272, 1921, U. S. Department of Interior, Bureau of Mines).

Effect	Parts per million (Benzene, xylene, toluene)
Slight symptoms after several hours of exposure.	1590 to 3130
Maximum concentration that can be inhaled for 1 hour without serious disturbance.	3130 to 4700
Rapidly fatal for even short exposure.	19,000

The following table of concentrations of benzole according to their effects and time of exposure is taken from the table drawn up in "Biochemical Engineering" (1935). (Cited by Browning, 1937, p. 11).

Concentration of benzol vapour in air (ppm)	Effects
19,000	Fatal in very short time.
3,000	Dangerous with exposures of 1/2 to 1 hour.
3,130 to 4,700	Maximum concentration for exposures of 1/2 to 1 hour.
1,570 to 3,130	Slight symptoms with exposures several hours.
100	Maximum concentration allowable.

DO 136627
CONFIDENTIAL

The following table, from [illegible] (191[illegible]), shows the progress of events with different concentrations in rabbits (cited by Browning, 19[illegible]7 p 17):

mg/l.	ppm	Time of exposure	Convulsions after	Lateral position after	Light narcosis	Deep narcosis	Further progress
57	1[illegible],000	3 hours	[illegible] hours	[illegible] minutes	-	5 hours	Slow recovery
46	1[illegible],500	[illegible] hours	[illegible] hour, [illegible]0 minutes	-	-	[illegible] hours	Death after 3 hours.
32	[illegible]9,000	70 minutes	5 minutes	9 minutes	40 minutes	50 min.	Slow recovery,

The lethal [illegible] concentrations are given in the following table taken from Browning, 1937 (p. 17):

Animals	Lethal Concentration mg/l.	ppm	Narcotic Concentration mg/l.	ppm	Author
Mice	43	1,000			Lauren (1939)
Mice			33	11,000	Kuhner (1921)
Cats	170	4,000	60	19,000	Lehmann (1914)
Cats			30	9,000	Meissner (1938)
Dogs	146	4,000			Luig (1913)
Rabbits	43 after 2 hours	1,000			Lehmann (1914)

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Single [illegible] to [illegible] Vapor
(Miscell[illegible] from the Lit[illegible])

Animal	Mg/l.	[illegible]	Time	Effect	Reference
Mice	15	[illegible],700	?	Onset of acute symptoms	[illegible]reiter, 19[illegible] Arch. Hyg., Berl. 108, 129
Cats	[illegible]	7,[illegible]	6 hours	Onset of acute symptoms	
	[illegible]	([illegible],300)	6 hours	Light narcosis	" "
	[illegible]	(1[illegible],100)	6 hours	Deep narcosis	" "
"Animals"	15-16	([illegible],700)	[illegible] minutes	"Jerking of leg muscles"	[illegible]nbousch (cited by Hamilton, 19[illegible], p. [illegible])
"Animals"	56	(17,[illegible])	[illegible] minutes	Convulsions	" "
"Animals"	56		10 minutes	Unconsciousness	" "
Dogs	[illegible]	(1[illegible],[illegible]00)	[illegible]0 minutes	Death	Hamilton, 1929, p. [illegible]
Cats	20	(6,[illegible]00)	[illegible] hours	Narcotic effect	Lehman
Cats	[illegible]0	(6,[illegible]00)	6 hours	Complete narcosis	(Cited by Hamilton, 1929 p. 456-457)
Cats	30	(1[illegible],100)	1[illegible] minutes	Narcotic effect	
Cats	60	(1[illegible],100)	1 hour	Complete narcosis	
Man	15	([illegible],700)	30 minutes	Listlessness and confusion	
Man	[illegible]0-30	(6 [illegible]00- [illegible], [illegible]00)	"Few hours"	Loss of consciousness	
Cavies	[illegible]0-[illegible]0	(6,[illegible]00- 15,900)	[illegible]0 minutes	Symptoms of acute poisoning	[illegible], 1935, J. [illegible] Chim. [illegible]1, 505-15.

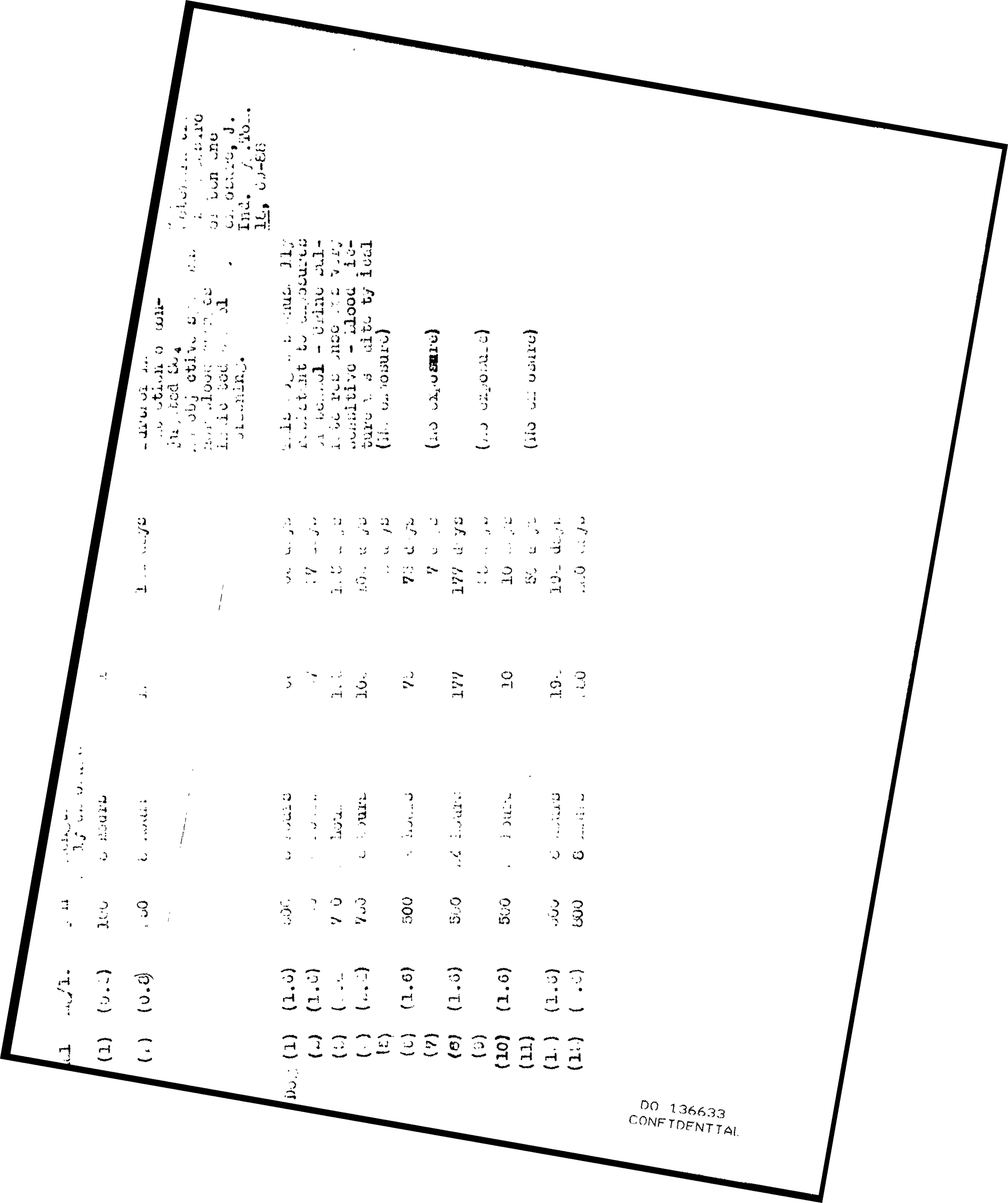
Repeated Exposures

There have not been a great number of experiments reported in which laboratory animals have been given repeated exposures to benzene vapors. An attempt has been made to present the available data in the following table. The data cited from the work of Yant et al and from McCord et al do not represent complete compilations of their work but does represent typical experiments.

CONFIDENTIAL
DO 136632

[illegible]

Animal	mg/l.	ppm	Length of daily exposure	No. of daily exposures	Total length of [illegible]	Effect	Reference
Rat	(7.8)	[illegible]40	18-20 hours	7	7 days	Conjunctivitis, lacrimation, coryza, redness, slight incoordination [illegible] twitching, [illegible] very weak but very excitable with clonic [illegible] body	Batchelor, 1926, Final Report on Benzol, N[illegible] Safety Council, p. 101.
	(5.3)	1055	18-20 hours	7	7 days	Incoordination, excitable, trembling.	"
	([illegible].6)	815	18-20 hours	7	7 days	No symptoms except slight [illegible] and [illegible]ness.	"
Dogs	7-10	[illegible]00-[illegible]100	6 hours		[illegible] 1/[illegible] [illegible]	Survived [illegible] without [illegible].	Lederer, 19[illegible] [illegible] (Browning, [illegible] p. 19)
Dog	([illegible].6)	800	8 hours	[illegible]54	[illegible]4 days	Typical blood picture of benzol poisoning.	Yant, [illegible] [illegible] Ind. [illegible] 18, 6[illegible]-68



DO 136633
CONFIDENTIAL

Repeated Exposure to Benzene

Animals	mg/l.	p.p.m	Length of daily exposure	Total length of exposure	Effect	Reference
Rabbit	(1.6)	500	7 hours	42 days	Leucopenia. Died	McCord, C. P. 1936, Benzol poisoning. The Industrial Health Conservancy Laboratories, Cincinnati, Ohio
		500	7 hours	54 days	Leucopenia. Erythrocytopenia. Died 6 days after termination of exposure.	
		500	7 hours	71 days	Leucopenia. Death.	
	(3.2)	1000	7 hours	42 days	Leucopenia. Death.	

Mode of Action

In acute poisoning the chief effect of benzole is upon the central nervous system, while in chronic poisoning the most severe degenerative changes occur in the hematopoietic system.

Quotations from several authorities are given below to substitute this statement.

"In acute benzole poisoning, the symptoms are due to a severely irritant and destructive effect upon the central nervous system, whereas in chronic benzole poisoning the relatively slight effects on the central nervous system are not at all comparable with the severity of the degenerative changes occurring in the hematopoietic system. In acute poisoning benzole thus acts as a convulsive neurotoxin and later as an asphyxiant narcotic" (Batchelor, J. J., 1927, The relative toxicity of benzole. Am. J. Hyg. 7, 276) [illegible], 1927, [illegible].

"In large doses, the effect of inhalation of benzole vapour upon animals is that of a nerve poison, with a characteristic neuro-irritant effect, as evidenced by muscle twitching, convulsions, general tremor, a state of hypertonicity of the body and [illegible] (Batchelor, 1927), shown in many cases by a peculiar rigid S-shaped formation of the tail. (Lazarew, 1929)

"A toxic action upon the heart is also postulated by Nahum and Hoff (1934), progressive anoxemia of the myocardium, and a sensitization of the myocardium to the effects of adrenalin, so that death may occur from ventricular fibrillation. (Cited from Browning, 1937, p. 17)

"___The effects of chronic benzene poisoning is to cause a loss of red blood corpuscles, resulting in profound anemia; a loss of the elements and substances in the blood which are concerned in blood clotting, resulting in hemorrhage; and a loss of white blood cells and of the substances in the blood serum which are concerned in defending the body against bacterial infection"(Hamilton, 1929, p. 470), (Hamilton, 1929, p. 475-479 presents a great deal of experimental evidence which substantiates the above statement).

From the work of a great number of investigators it is certain that benzole is a leucotoxin (evident particularly in chronic exposures), destroying not only the circulating leucocytes in the blood, but also the parenchymatous cells of the bone-marrow, spleen and lymph glands. Apparently this destructive effect is more pronounced on the myelocytic than the lymphatic elements. In addition there is a less obvious effect on the erythrocytes, due to injury of the erythroblastic tissue in the bone-marrow and an initial stimulating effect on the bone-marrow with a resulting leucocytosis.

Even though we have adequate evidence for benzole's action upon the hemato-poietic system, the exact nature of this action, its specificity and the point of initial attack are still undetermined.

Field Studies

Recently a very complete report of carefully conducted study of industrial benzene exposure has been published as follows:

Dorwitch, H. and Elkins, H. B. Chronic Exposure to Benzene (Benzol). I. The Industrial Hygiene Aspects. J. Ind. Hyg. & Tox. 41, 348-350, 1959.

Hunter, W. T. Chronic Exposure to Benzene (Benzol). II. The Clinical Effects. J. Ind. Hyg. & Tox. 41, 351-354, 1959.

Mallory, T. B., Hall, H. and Brickley, W. J. Chronic Exposure to Benzene (Benzol). III. Histologic Studies. J. Ind. Hyg. & Tox. 41, 355-377, 1959

Several clinical and laboratory studies are [illegible] the authors. The latter is in [illegible] and has carefully [illegible] of benzene. Further, histologic material from 10 cases with a history of chronic benzene exposure was studiously examined.

The [illegible] poisoning appears to manifest in workers exposed to concentrations [illegible] 7 ppm (1.460). Exposure to the latter was the concentration found to be over 800 ppm in most cases it was much below this figure.

The clinical (including laboratory) examination of the 89 benzene workers led to the following conclusions (p. 354):

"Depending on the degree and duration of exposure, an analysis of the blood picture indicates that benzene may bring about: polycythemia; leukemia or leucemoid blood pictures (either lymphatic or myeloid); eosinophilia; macrocytosis or microcytosis; the presence of immature marrow elements in an otherwise normal blood.

"The early diagnosis of poisoning depends upon a close study of the blood picture rather than upon the existence of a leucopenia.

"[illegible] may [illegible] restricted cases of poisoning.

"Women [illegible] more susceptible than men, and [illegible].

"The first signs of poisoning may appear with the onset of an infection, long after exposure has ceased.

"It is doubtful whether any concentration of benzene greater than [illegible] over long periods of time"

DO 136638
CONFIDENTIAL

The fact that the first signs of benzene poisoning may appear but the onset of an infection long after exposure has ceased is of particular interest. We may quote the authors as follows (p. [illegible]):

"The most unexpected observation made in this study is that the first clinical symptoms and signs of chronic poisoning may appear long after exposure has ceased. Case [illegible] from Factory [illegible] was the first instance of this, and the fact was subsequently confirmed when case 79 from an entirely different factory entered the hospital. Both of these cases showed no signs of poisoning until the onset of [illegible] merely a minor infection. The disastrous sequelae which then occurred suggest a new concept of marrow function: that of an injured marrow sufficiently compensated to carry on during normal health, but decompensating at the onset of even slight sepsis. The analogy is similar to that of a damaged heart at rest [illegible]. [illegible] industrial compensation [illegible] poisoning [illegible], long [illegible] acute leucemia (27) [illegible] problems of compensation even more far-reaching in nature--[illegible], if future observations confirm the suspected causal relationship between certain cases of this [illegible] and chronic benzene poisoning."

A summary of the histological findings in the bone marrow and spleen is given on page 674.

Most important is the fact that the pathological changes continue to develop after the exposure has ceased. We may quote the authors as follows:

"No discussion of the anemias of benzene poisoning can be complete without mention of the close similarity of many of these hyperplastic marrows, composed predominantly of immature erythroblastic elements, to the bone marrows described by Hartland (19--) in chronic radium poisoning. A still more surprising, though probably accidental parallelism exists in the prolonged latency between exposure and the development of symptoms or detectible signs frequently observed in the two conditions. The authors can do no more than express their sentiment that a simple volatile organic chemical, readily eliminated via the respiratory tract after initiating certain metabolic changes which can progress for months and even years after the exposure has ceased."

There is also some evidence that benzene exposure to man may produce tumors. Again the authors:

"Also suggestive to anyone who has studied even superficially cases of true hyperplastic type which have been presented in this article are the evidences of what, for want of a better term, may be called neoplastic tendency. The degree of this basic, cellular growth is judged by the number of mitotic figures, by development of cells having no counterpart in normal tissues but common to a variety of malignant tumors and phenomena characteristic of

neoplasia which the authors have never heretofore met in such marked degree in non-neoplastic states. Certainly no more favorable conditions for the development of neoplasm can be imagined than prolonged and intense stimulation of reproductive activity and simultaneous arrest of maturation.

"The evidence that chronic exposure to benzene produced leukemia in human beings is still incomplete. But it is accumulating and the case and the volume which demand serious consideration."

Toxicological Significance of Benzene

Many additional cases of chronic industrial exposure to benzene have been made. Some of the better ones given below:

Browning, Toxicity of Industrial Solvents, His Majesty's Stationery Office, London, 1937. 7-31.

Middleton, Industrial Poisons in the United States. The Macmillan Company, 1934, 450-454.

Hamilton, Benzene (benzol) Poisoning. Arch. Path. 11, 411-413, 601-607, 1931.

Final Report of the Committee on Benzol. National Safety Council, 1926.

The review in Federally (Toxicology, Industrial Medicine, Chicago, 1937, p. 730-768) is very misleading. He has completely confused the literature on benzene (benzol) and benzine. In no case is this review of benzene toxicology to be followed.

From the reviews the impression is gained that a great many cases of benzene poisoning have occurred in industry and that there have been a considerable number of deaths. Since in only few instances is there any indication of the severity of exposure, it would not be advisable to make a careful study of all these cases. However, the record of so many cases emphasized the definite industrial hazard presented by benzene.

The evidence given by the recent clinical and pathological studies (J. Ind. Hyg. & Tox. 21, 1939) emphasizes the insidious nature of benzene poisoning with its destruction of the cellular action.

Allowable Limits

The maximum allowable concentration above which toxic symptoms may be expected to develop, was established by the National Safety Council (1939) as 100 ppm. The concentration which produced and resulted in [illegible] appeared to be 10,000 - 20,000 ppm (Greenburg, 1937, p. 12).

Recent workers (Lanton, H. F. Chronic Exposure to Benzene (Benzol). II. The Clinical Aspects. J. Ind. Hyg. and Tox. 21, 331-354, 1939) states "It is doubtful whether any concentration of benzene greater than 100 p.p.m. can be safe for a long period of time."

Some Established Limits

	ppm Benzol
U. S. Public Health Service	100
Connecticut Health Department	100
California Ind. Acc. Comm.	100
Wisconsin Ind. Comm.	100
Russian Authorities	15-35
Suggested for Massachusetts	75

(Commonwealth of Massachusetts, Dept. of Labor and Industries, Division of Occupational Hygiene. May, 19[illegible])

Significant Articles and Reviews on Toxicology of Benzene

(1) Browning, E., Toxicology of Industrial Solvents, His Majesty's Stationery Office, London, 1937, 7-[illegible].

(2) Hamilton, A., Industrial Poisons in the United States. The MacMillan Company, 19[illegible], [illegible].

(3) Hamilton, A., Benzene (Benzol) Poisoning. Arch. Path. 11: [illegible], [illegible]-[illegible]37, 19[illegible]1.

(4) Final Report of the Committee on Benzol. National Safety Council, 19[illegible].

(5) McCord, C. [illegible] Benzol (Benzene) Poisoning. The Industrial Health Conservancy [illegible] Series. Cincinnati, 19[illegible].

(6) Bowditch, M. and Elkins, H. B., Chronic Exposure to Benzene (Benzol). I. The Industrial Aspects. J. Ind. Hyg. & Tox. 21, [illegible]1-[illegible] (19[illegible])

(7) Hunter, [illegible] T. [illegible] exposure to [illegible] (Benzol). II. The Clinical [illegible]. J. Ind. Hyg. & Tox. 21, [illegible]1-[illegible] (1[illegible])

(8) Mallory, [illegible], [illegible]ll, [illegible] and Brickl[illegible], [illegible]. [illegible]. Chronic [illegible] to [illegible] ([illegible]ol). III. [illegible]ologic Results. J. Ind. [illegible] 21, [illegible] (19[illegible])

[illegible]

DO 136644
CONFIDENTIAL