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Subject A COMPARATIVE STUDY OF THE VAPOR TOXICITY OF BENZENE, CARBON TETRACHLORIDE, AND ETHYLENE DICHLORIDE., LITERATURE SURVEY.

(A summary article supplementary to the individual reports on these three compounds.)

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Single Exposures

It is almost impossible and certainly impractical to make detailed comparisons of single exposure experiments conducted by different investigators using varying techniques. The following table presents, in most general terms, the concentration ranges of benzene, carbon tetrachloride and ethylene dichloride which produce a given physiological response:

Single Exposures

Effects	Benzene, p.p.m.	CCl_4, p.p.m.	Ethylene dichloride, p.p.m.
Fatal in very short time.	19,000	48,000-63,000	100,000-200,000
Dangerous with exposures of 1/2 to 1 hour.	3,000	24,000-32,000	10,000-60,000
Maximum concentration for exposures of 1/2 to 1 hour.	3,130-4,700	4,000-6,000	3,500-6,000
Slight symptoms with exposures of several hours.	1,570-3,130	1,600	1,000
Established limit for repeated exposures.	100 (or less)	100	100

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It is of particular importance to note the great differences in concentrations required to cause death in a very short time. As very acute poisons, the compounds can definitely be arranged in the order benzene > carbon tetrachloride > ethylene dichloride. However, at the lower concentrations there is much less difference in the physiological response evoked.

A study of the data presented in the individual papers on these compounds will bear out this general conclusion. (Note:- It is definitely inadvisable to try to make too strict a comparison of the data presented.)

It should be remembered that in any vapor toxicity experiment there are four factors which should be considered:

1. Species of animal used (i.e., rabbit, dog, cat, rat, guinea pig, mouse, monkey, man.).
2. Individual animal variation within species, so-called sensitivities and idiosyncrasies.
3. Concentration of vapor.
4. Length of exposure.

Any comparisons that are made should take into account these four factors.

It should also be noted that we have used two methods of expressing the concentration of vapors: parts per million, meaning volumes of vapor per million volumes of air; and mg./liter, meaning milligrams of vapor per liter of air. The temperature and barometric pressure should always be stated, but if it is not, it is commonly assumed (sometimes wrongly) that the temperature is 25° C. and pressure 760 mm. mercury.

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(Henderson and Haggard, page 56.) Thus:

Benzene ----- 1 mg./liter = 313 p.p.m.
CCl_4 -------- 1 mg./liter = 159 p.p.m.
Ethylene dichloride - 1 mg./liter = 247 p.p.m.

Repeated Exposures

The most extensive work with repeated animal exposures has been done by the Smyths on carbon tetrachloride.

The work by the various authors cited in the benzol paper does not compare in thoroughness or completeness with that of the Smyths on carbon tetrachloride.

No repeated animal exposure experiments have been conducted with ethylene dichloride.

It is impossible to make a direct comparison of the work on carbon tetrachloride with that of benzene since the rat is the only species that was studied by both the investigators of carbon tetrachloride and the investigators of benzene. In this case the highest concentration used by Smyth was 400 p.p.m. carbon tetrachloride while the lowest used by Batchelor was 1035 p.p.m. benzene. Furthermore, the length of the daily exposure used by Smyth with carbon tetrachloride was 8 hours, while that used by Batchelor for benzene was 18 to 20 hours.

Nevertheless, a study of the Smyths' work on carbon tetrachloride together with that on benzene by Batchelor; Lederer; Yant, et al.; and McCord indicates that benzene is definitely more toxic than carbon tetrachloride upon repeated exposures. The experiments with rabbits, dogs,

and rats exposed to benzene show that upon repeated exposure the typical symptoms, particularly the blood responses, become evident, and usually increase in severity until death results. In the case of carbon tetrachloride the apparent "acclimatization" of the animals to repeated exposures is significant.

Mode of Action

The following table summarizes the characteristic action of each of the three compounds:

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Mode of Action

Compound	Central nervous system	Hematopoietic system	Liver	Kidney	Lung	Heart	Corneal opacity	"Acclimatization"
Benzene	Marked in acute poisoning.	Marked in chronic poisoning.				Cardiac damage postulated by a few workers.		None.
CCl_4	Questionable.		The primary site of injury.	Involved if exposure is sufficiently severe.				Reported for experimental animals and man.
Ethylene dichloride.			Marked effect (Muller, 1950). Unconfirmed by later workers.	Secondary to lung involvement.	Marked damage in acute poisoning.		Reported by many investigators.	No reports.

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It should be re-emphasized that in acute benzene poisoning the chief effect is upon the central nervous system while in chronic benzene poisoning the major effect is upon the hematopoietic system. There is no evidence that "acclimatization" (See Hunter, J. Ind. Hyg. and Tox. 21: 354 (1939)) occurs upon repeated exposure to benzene but, rather, that there is a definite tendency fof degenerative changes to progress even after the exposures are discontinued.

In the benzene paper (under "Field Studies", page 11-15) it is pointed out (giving quotations) that:

1. The first signs of benzene poisoning may appear with the onset of an infection long after exposure has ceased.
2. The pathological changes may continue to develop after the exposures have ceased.
3. Chronic benzene poisoning may (possibly) produce leucemia.

This is definitely in contradistinction to carbon tetrachloride, since there is ample evidence to show that regenerative processes occur in the liver and kidney even while the exposures are in progress and that recovery is usually rapid following the discontinuation of exposure. Thus: "An animal continuously exposed to small amounts of carbon tetrachloride soon regenerates originally damaged liver cells and somewhat later regenerates damaged kidney cells, the regenerated or entirely new cells being more resistant to the vapors than were the original cells. It is concluded from this that in most cases men continuously exposed to small concentrations of carbon tetrachloride increase their resistance rather than increasing

their susceptibility. This contrasts strongly with the action of benzene, the safe concentration of which is also set at 100 p.p.m., since with that solvent injury may be progressive even after exposure is stopped." (Quoted from Comments and Conclusions of article by Smyth and Smyth, Safe Practices in the Industrial Use of Carbon Tetrachloride, J. A. M. A. 107: 1683-1687 (1936).)

"It is definitely shown that an animal continuously exposed to amounts of carbon tetrachloride from 50 to 400 p.p.m. soon regenerates originally damaged liver cells and somewhat later regenerates damaged kidney cells while the exposure continues, the regenerated cells being more resistant than the original cells. It is believed on the basis of physical examination of workmen that the same is true of humans. It is argued from this that in most cases men working with carbon tetrachloride under reasonable conditions of ventilation and care increase their resistance rather than increasing their susceptibility. This contrasts strongly with benzene, the safe concentration of which is also set at 100 p.p.m. (Final Report of the Committee on Benzol, Nat. Safety Council, May, 1926), since with that solvent, injury is at times pregressive even after exposure is stopped, making carbon tetrachloride the safer of the two for industrial use." (Quoted from the conclusions and discussion of the article by Smyth, Smyth and Carpenter, The Chronic Toxicity of Carbon Tetrachloride; Animal Exposures and Field Studies, J. Ind. Hyg. and Tox. 18: 277-298, 1936.)

While the data is not nearly as extensive in the case of ethylene dichloride, the nature of its action would indicate that the behavior of animals exposed to its

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vapor should be similar to the behavior of carbon tetrachloride animals and quite unlike the benzene animals. There have been no reports dealing specifically with "acclimatization" to ethylene dichloride vapors.

Field Studies

Smyth, et al. (J. Ind. Hyg. and Tox. 18: 277-298 (1936)) made a careful study of 96 men exposed to carbon tetrachloride in industry. None of these could be considered seriously or even unmistakenly injured by the solvent vapors.

In contrast to these findings with carbon tetrachloride, the recent study of 89 benzene workers (J. Ind. Hyg. and Tox. 21: 321-377 (1939)) shows that symptoms of benzene poisoning may be found in workers exposed to well below 75 p.p.m. They conclude that "it is doubtful whether any concentration of benzene greater than zero is safe over a long period of time."

No comparable field studies have been made on ethylene dichloride, but the scarcity of published cases of ethylene dichloride poisoning indicates its relatively non-hazardous nature.

Smyth in his survey of the literature for 1937 and 1938 gives the following tabulations:

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Literature Survey 1937-1938
Poisonings from Vapor Exposures

Accidents and Repeated Exposures Considered Together

(According to Smyth, Report of the Committee on Volatile Solvents to the Industrial Hygiene Section of the American Public Health Association, (1939))

Material Blamed	Cases	Fatalities
Benzene and homologs	148	30
Carbon Tetrachloride	11	0
Ethylene dichloride	5	0

It would seem that the number of cases of poisoning reported, together with fatalities, should be a good index of the industrial hazard involved in the use of a volatile solvent. A survey of the literature for 1937-1938 emphasizes the industrial hazard of benzene as compared with Carbon Tetrachloride or Ethylene Dichloride.

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Literature Survey 1937-1938
Vapor Concentrations in Industry

(According to Smyth, H. F., Jr., Report of the Committee on Volatile Solvents to the Industrial Hygiene Section of the American Public Health Association (1939))

Vapor	Industry	No. of tests	ppm Ave.	ppm Mim.	ppm Max.
Benzene	Asbestos impregnation			520	550
Benzene	Asbestos impregnation				80
Benzene	Shoe Mfg.	23	184	12	415
Benzene	Wool & Worsted	7	190	5	515
Benzene	Rubber	6		85	365
Benzene	Paper Coating	63		0	575
Benzene	By-product Coke				400
CCl_4	Wool & Worsted	2	55		
CCl_4	Rubber Goods	4		0	20
CCl_4 or trichloroethylene	Fur Cleaning	83	50	5	330
CCl_4 or trichloroethylene	Fur Cleaning	12	81	5	195
Ethylene dichloride	Wool & Worsted	3	4	0.4	5

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Comparative Toxicological Significance of Benzene, Carbon Tetrachloride and Ethylene Dichloride

If the opinions of several State and National Public Health workers (Smyth, Ind. Med., 1935, 1-4, quoted in Carbon Tetrachloride paper p. 7-9) as well as other recognized toxicologists are compared with the opinions of Bowditch and Elkins, of the Division of Occupation Hygiene, Massachusetts Department of Labor and Industries, Boston, Massachusetts (J. Ind. Hyg. & Tox. 21, 321-330 (1939)), Hunter of the Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts. (J. Ind. Hyg. & Tox. 21, 331-354 (1939)), and Mallory, Gall and Brickley of the Department of Pathology and Bacteriology, Massachusetts General Hospital, and the Office of the Medical Examiner for Suffolk County, Northern Division, Boston, Massachusetts (J. Ind. Hyg. & Tox. 21, 355-392 (1939)), there can be no doubt as to the relative toxicity of Carbon Tetrachloride and benzene. The preponderance of opinion is definitely favorable toward carbon tetrachloride.

While there is only meager data available concerning ethylene dichloride, the Public Health workers who did the experimental work on acute ethylene dichloride exposures (Public Health Reports 45, 225-239 (1930) Reprint #1349) give no indication of its being more hazardous than carbon tetrachloride but, rather, indicate that according to their experiments, it may be somewhat less so.

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Likewise the comparative study of the "Mode of Action" of these compounds as well as "Field Studies" point to the same general conclusions that benzene is definitely the most hazardous of the group.

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