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Y AND CONCLUSIONS

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TCE-(H)

The Problem of Trichloroethylene in Occupational Medicine

Trichloroethylene Metabolism and Its Effect on the Nervous System Evaluated as a Means of Hygienic Control

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and
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Trichloroethylene is widely used all over the world as a solvent for fats and other organic compounds. It is employed for degreasing, cleaning, and extracting purposes and recently also as the raw material for organic syntheses. From the technical point of view it has excellent properties—powerful solvent action and a convenient boiling point (87 C); it is incombustible, is markedly inert chemically, and has also suitable biological properties; owing to its remarkable metabolism in the organism, it is not toxic to the liver. Like other volatile solvents with fat affinity, it is a powerful anesthetic drug and nerve poison.

The toxicology of trichloroethylene has been extensively studied in Europe and America: many investigators undertook research on its narcotic and toxic effects from the clinical, hygienic, and toxicological aspects. The acute and chronic toxicity was studied in animals and man. Inasmuch as the biological effect of every poison is displayed by the mutual reaction between organism and toxic agent, considerable research was done by biochemists who were able, owing to the Fujiwara color reaction * given by some halogen compounds with pyridine and alkali, to follow fairly easily the effect of the organism upon trichloroethylene, that is to say, the metabolism of trichloroethylene and the elimination of both trichloroethylene and its products.

Received for publication March 7, 1955.

* References 1 and 2.

PART I

In 1933 Brüning and Schnetka [3] found that the urine of persons exposed to trichloroethylene vapors gives with pyridine and alkali a color reaction like that of trichloroethylene and suggested the elimination of this hydrocarbon by urine. In 1938 Barrett and Johnston † demonstrated trichloroacetic acid in the urine of dogs narcotized with trichloroethylene. They were unable to explain its origin. Trichloroactic acid was isolated in the form of its piperazine salt. Powell [6] brought additional proof of the matter by identifying this compound in the urine of persons on whom an operation was performed under trichloroethylene anesthesia; she also demonstrated the slowness of its elimination and stressed the importance of the Fujiwara color reaction for the check-up of persons exposed to trichloroethylene in their work. With Paykoç [7] she followed the curious slow elimination of trichloroacetic acid after intravenous injection of its sodium salt and derived a formula for its blood level.

$$c = \frac{2}{3} e^{-0.0085\ t} + \frac{1}{3} e^{-0.13\ t}$$

The validity of the formula was confirmed (for the concentrations studied by Powell and Paykoç) by Bardodĕj and Krivucová ‡ who followed the elimination of trichloro-

† References 4 and 5.

‡ Bardodĕj, Z., and Krivucová, M.: Unpublished data.

acetic acid in the urine of both persons to whom chloral hydrate was administered per os and persons given trichloroethylene inhalations. Bardoděj, Chlumský, and Krivucová § followed trichloroacetic acid elimination in a case of accidental severe acute trichloroethylene intoxication. The results are illustrated in Graph 1. The deviation from the original exponential slope of the elimination curve after reaching the elimination maximum on the third day (when trichloroacetic acid was still being produced by the organism) is explained by these investigators by suggesting the influence of a mechanism operating with a slower action than that of the simple passage of trichloroacetic acid through the kidney filter—most probably a slow desorption of trichloroacetic acid from proteins. The acid continued being eliminated for about three weeks. Vyskočil ‖ observed after trichloroethylene ingestion a somewhat slower trichloroacetic acid elimination, which he explained by a prolonged trichloroethylene resorption from the gastrointestinal tract, its sluggish metabolism being toned down by the liver filter. Bardoděj and Krivucová ¶ found that the amount of trichloroacetic acid in the daily urine increased with increased liquid intake. The same, though attenuated, effect was observed after purine diuretics. Pyrazolone antidiuretics increased trichloroacetic acid concentration in urine portions, probably through an increased retrograde resorption of water in the tubuli. According to Ahlmark and Forssman,[8] at the most two-thirds of sodium chloroacetate administered to rats is excreted, while in man, according to Powell,[7] the quantity is likely to be higher (at least two-thirds of the injected amount).

In 1949 Butler,[9] who started by studying the metabolism of chloral hydrate,# found another metabolite of trichloroethylene in the form of trichloroethanol and isolated its glucuronide from dog urine. Conjugation of trichloroethanol with glucuronic acid and elimination of the formed urochloralic acid are rapid. Trichloroethanol was demonstrated in the urine of persons exposed to trichloroethylene by Souček and Vlachová * and by Bardoděj, Chlumský, and Krivucová.† Increased glucuronide elimination in persons exposed to high trichloroethylene concentrations was observed by Bardoděj, Berka, Chalupa, Nesvadba, and Vyskočil ‖

These investigators suggested also the probable formation of monochloroacetic acid,[12] demonstrated in 1954 chromatographically by Souček and Vlachová.‡

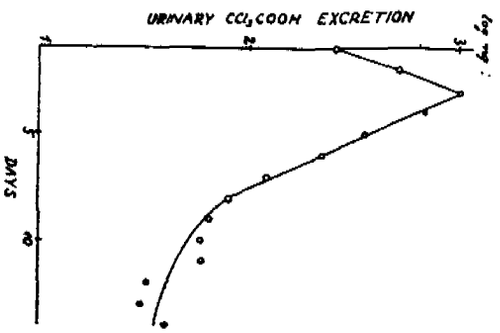

Fig. 1.—Urinary excretion of trichloroacetic acid.

In the same year Bardoděj and Krivucová,§ considering the spontaneous decarboxylation of trichloroacetic acid and its sodium salt in both water solutions and urine samples, suggested another metabolite—chloroform, occurring in slight amounts. It is interesting to note that it was Liebreich [13] who in 1869 considered chloroform formation from chloral hydrate possible and tried

§ Bardoděj, Z.; Chlumský, J., and Krivucová, M.: Severe Acute Trichloroethylene Intoxication in Industry, Časop. lék. česk. **44**:1004-1008, 1955.

‖ Vyskočil, J., and Berka, I.: Trichloroethylene. Praha, Státního Zdravotnického Nakladatelstvi, 1955.

¶ Bardoděj, Z., and Krivucová, M.: Unpublished data.

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* Souček, B., and Vlachová, D.: Further Trichloroethylene Metabolites in Man, Prac. lék. **6**:330-332, 1954.

† Bardoděj, Z.; Chlumský, J., and Krivucová, M.: Severe Acute Trichloroethylene Intoxication in Industry, Časop. lék. česk. **44**:1004-1008, 1955.

‡ Souček, B., and Vlachová, D.: Further Trichloroethylene Metabolites in Man, Prac. lék. **6**:330-332, 1954.

§ Bardoděj, Z., and Krivucová, M.: Contribution to the Question of Further Trichloroethylene Metabolites Which Could Give a Positive Fujiwara Reaction in Urine, Prac. lék. **7**:97-98, 1955.

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Inasmuch as both trichloroac chloralic (trichloroethanolglucu are metabolites of trichloroethy as of chloral hydrate, Butler thought chloral hydrate an product in trichloroethylene m the body. But he was unable to it in dogs' blood after trichloroet lation. Failure in this expe experienced also by Bardoděj cová ‖ who conducted a similar human urine.

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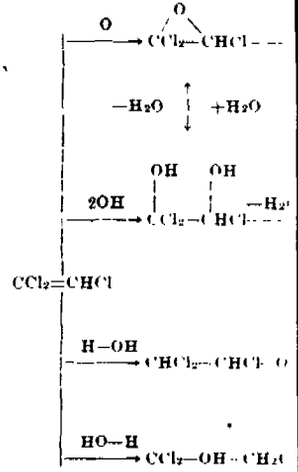
‖ Bardoděj, Z., and Krivucová, lished data.

¶ Bardoděj, Z., and Krivucová, M. to the Question of Further Trichloro tabolites Which Could Give a Posit Reaction in Urine, Prac. lék. **7**:97-98.



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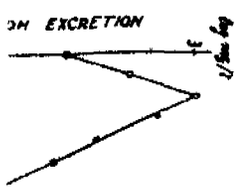

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—erroneously—to explain the action of this hypnotic on that basis.

Inasmuch as both trichloroacetic and urochloralic (trichloroethanolglucuronic) acids are metabolites of trichloroethylene as well as of chloral hydrate, Butler [9] correctly thought chloral hydrate an intermediate product in trichloroethylene metabolism in the body. But he was unable to demonstrate it in dogs' blood after trichloroethylene inhalation. Failure in this experiment was experienced also by Bardoděj and Krivucová ‖ who conducted a similar research on human urine.

Bardoděj and Krivucová ¶ did not find any additional substances in urine which would give the Fujiwara color reaction after acid hydrolysis. The ratio of inorganic and organic sulfates was not altered after trichloroethylene inhalation.[12]

We think the following schema the most likely explanation of the curious trichloroethylene alteration in the body. We are still unable to decide which of the suggested courses is really taken in the body in the formation of the unstable 1,2,2-trichlorovinyl alcohol, the production of which is the most probable explanation for the chlorine-atom migration.

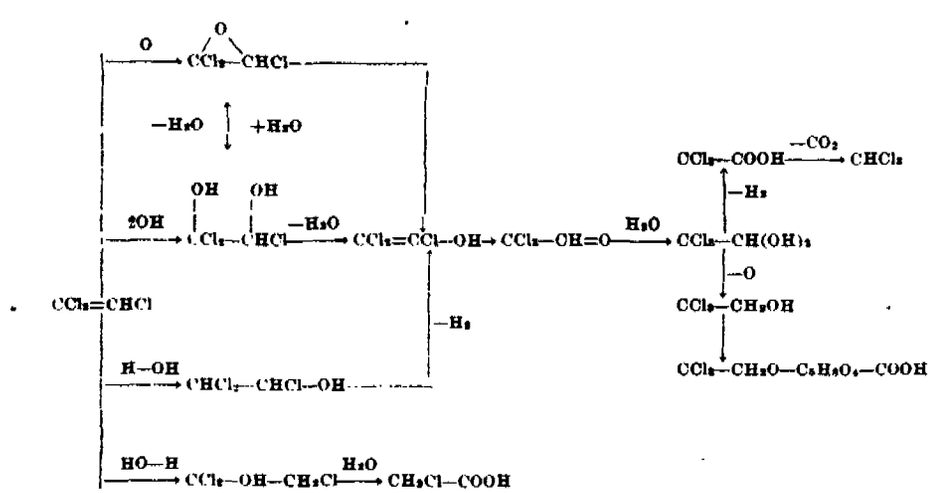
Study of the quantitative balance of inhaled trichloroethylene in man was conducted by Teisinger and co-workers [14] and previously in rats by Ahlmark and Forssman.[8] Their results coincide in that about half of the inhaled trichloroethylene is resorbed. According to Souček. Teisinger, and Pavelková, 16% of the resorbed trichloroethylene is converted to trichloroacetic acid. According to the Swedish investigators, the amount is from 6% to 16%. Barrett and Johnston thought that the quantity of resorbed trichloroethylene converted to trichloroacetic acid is 5% to 8%. Forssman and Holmquist [15] found in rats 1.2% to 4.2% of inhaled trichloroethylene changed into trichloroacetic acid. Bardoděj and Krivucová # thought that in high trichloroethylene concentrations, and with prolonged exposure, the amount of trichloroethylene changed into trichloroacetic acid decreases. The results of serial studies in industry showed the amount of trichloroethylene changed into trichloroacetic acid to be about 5% to 8% of the inhaled quantity.*

‖ Bardoděj, Z., and Krivucová, M.: Unpublished data.

¶ Bardoděj, Z., and Krivucová, M.: Contribution to the Question of Further Trichloroethylene Metabolites Which Could Give a Positive Fujiwara Reaction in Urine, Prac. lék. 7:97-98, 1955.

Bardoděj, Z., and Krivucová, M.: Exposure Tests: I. Trichloroethylene, Prac. lék. 7:217-220, 1955.

* Bardoděj, Z., and Krivucová, M.: Trichloroethylene Hazard in Prague Dry-Cleaning Establishments, Čs. hyg. epid. mikrob. immun. 4:90-94, 1955.



Metabolism of trichloroethylene

Butler [9] found in experiments on dogs that the amount of trichloroethanol from inhaled trichloroethylene is larger than that of trichloroacetic acid. The results were confirmed in man by Souček and Vlachová.† In following the quantitative change of chloral hydrate in the body, Bardoděj and Krivucová ‡ found in the urine a 1 : 2 total molecular ratio of trichloroacetic and trichloroethanolglucuronic acids after a single 0.5 gm. dose of chloral hydrate: after higher doses the ratio increased to 1 : 4.

Occupational hazards in industrial plants using trichloroethylene are estimated by the following hygienic measures:

1. Trichloroethylene vapor determination in the air. This serves to ascertain whether or not the allowed concentration limit has been passed, thus making sure that the decree of the Ministry of Health concerning allowable limiting concentrations of toxic substances in working atmospheres has not been broken.

2. Trichloroacetic acid determination in the urine of employees. This is a means of estimating the average trichloroethylene concentration in the atmosphere.

3. Determination of the so-called organic chlorides in urine. We deem this theoretically sounder than the trichloroacetic acid determination, as it permits one, when the procedure is properly chosen, to take into account even the trichloroethanol freed from the glucuronide by acid hydrolysis. The procedure has one drawback—it is considerably more involved than the simple trichloroacetic acid determination by the Fujiwara color reaction.

Procedures under Measures 1 and 2 are currently used in our laboratory in the following modified forms.

Trichloroethylene Determination in Atmosphere

Air samples are sucked through two absorption vessels with spiral capillaries or else through a porous plate of sintered glass filled with 5 ml. of pyridine. At a suction rate of 1 liter per 10 minutes, the intake in the first vessel is practically quantitative (90%). Colorimetric determination is conducted immediately after return to the laboratory.

Reagents.—Pyridine (analytical grade); 0.05 N sodium hydroxide solution.

Procedure.—Four milliliters of pyridine with the absorbed trichloroethylene is pipetted into a test tube (or else an aliquot portion of the sample is made into 4 ml. with pyridine); 1 ml. of 0.05 N sodium hydroxide is added, shaken, and heated for 15 minutes in a water bath at 70 C. then the mixture is cooled with cold water, 1 ml. of purified water is added, and colorimetric determination is conducted with use of the blue filter. The produced color remains stable for 15 minutes.

Trichloroacetic Acid Determination in Urine

Daily urine samples collected at the end of the week are taken for analysis.

Reagents.—Pyridine (analytical grade); 20% sodium hydroxide solution.

Procedure.—Two milliliters of urine is pipetted into a test tube; 5 ml. of 20% sodium hydroxide solution is added, and the mixture is thoroughly shaken; 10 ml. of pyridine is next added, and the mixture is again shaken until it is milk turbid; the mixture is then heated for 15 minutes in a water bath at 70 C, after which it is cooled with cold water. From the pyridine (upper) layer, 5 ml. is pipetted into another test tube; 2 ml. of purified water is added, mixed, and colorimetric determination is conducted with use of the green filter against the empty sample processed like the analyzed urine which is replaced with 2 ml. of purified water. The produced color remains stable for 15 minutes.

With higher concentrations it is imperative to take an aliquot urine sample for the analysis; with very low concentrations the colorimetric determination is conducted against a urine sample free of Fujiwara-positive substance and processed like the urine with unknown trichloroacetic acid content. Thus, possible interfering effects of urine pigment are eliminated.

The question of trichloroacetic acid concentration ratio in urine and the level of atmospheric trichloroethylene has been studied by several investigators. Frant and Westendorp [16] concluded that we may expect 200 mg. of trichloroacetic acid in urine under a maximum allowable concentration (MAC), that is to say, 100 ppm (0.53 mg. per liter). Elkins [17] found 160 mg. and less. Bardoděj and Krivucová § reported that at 0.4 mg. of trichloroethylene in 1 liter of air—which is the limit concentration in our country—employees working in such an atmosphere

† Souček, B., and Vlachová, D.: Further Trichloroethylene Metabolites in Man, Prac. lék. **6**:330-332, 1954.

‡ Bardoděj, Z., and Krivucová, M.: Unpublished data.

§ Bardoděj, Z., and Krivucová, M.: Exposure Tests: I. Trichloroethylene, Prac. lék. **7**:217-220, 1955.

excreted about 140 acid per liter of urin the 48-hour working compared with the United States and u the burden of employ far as the standard \

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Higher trichloroac in urine in relation t centration in the air Kylin, and Nyström 500 mg. of trichloroac conducted experimen posed continuously t days only); higher re tered in Teisinger's l of Ahlmark and For were arrived at under

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In conclusion, we t the urine trichloroac to be more than 160 the allowed standard. United States and Cz certainly been overre tration of the noxious siderably, even smalle be regarded as suspic point of view.

Evaluation of the tr by way of determinati in urine has not yet oped in our country; this point should be monograph of Elkins.

‖ Bardoděj, Z., and I Tests: I. Trichloroethy 1955.

excreted about 140 mg. of trichloroacetic acid per liter of urine. Taking into account the 48-hour working week in our country as compared with the 40-hour week in the United States and using the Haber relation, the burden of employees is about the same so far as the standard MAC is observed:

Czechoslovakia .....0.40×48=19.20
U. S. A. (100 ppm)...0.53×40=21.20

Higher trichloroacetic acid concentrations in urine in relation to trichloroethylene concentration in the air are given by Friberg, Kylin, and Nyström [18] (at 100 ppm 250 to 300 mg. of trichloroacetic acid). The authors conducted experiments on persons not exposed continuously to trichloroethylene (five days only); higher results were also encountered in Teisinger's balance [14] and in reports of Ahlmark and Forssman [8] whose results were arrived at under laboratory conditions.

Bardodéj and Krivucová ‖ and Elkins [19] thought the difference in percentage to be dependent on trichloroethylene concentration in the air. The same relation can partly be derived from the paper of Frant and Westendorp.[16] Without doubt individual quantitative differences may be noticed in trichloroethylene metabolism within certain limits, the causes for that being both endogenous and exogenous (nutrition, outdoor activity, etc.).

In conclusion, we think that, upon finding the urine trichloroacetic acid concentration to be more than 160 mg. per liter of urine, the allowed standard, which is valid for the United States and Czechoslovakia, has most certainly been overreached. As the concentration of the noxious element may vary considerably, even smaller concentrations should be regarded as suspicious from the hygienic point of view.

Evaluation of the trichloroethylene hazard by way of determination of volatile chlorides in urine has not yet been sufficiently developed in our country; information regarding this point should be sought in the excellent monograph of Elkins.[19]

‖ Bardodéj, Z., and Krivucová, M.: Exposure tests: I. Trichloroethylene, Prac. lék. 7:217-220, 1955

TABLE 1.—*Number of Persons Suffering Damage to Health in Relation to Urine Trichloroacetic Acid Concentration in Urine According to Statistics of Ahlmark and Forssman*

Trichloroacetic Acid Concentration in Urine, Mg./L.	Average (Theoretical) Trichloroethylene Concentration in Air, Mg./L.—Graph 2	Persons with Signs of Intoxication, No.
20	0.05	0
40-75	0.1-0.19	50
100	0.25	100
300	0.50	Medical leave advised

The correlation between trichloroacetic acid concentration in urine and the working hazard of employees was studied by several authors. Ahlmark and Forssman [20] found very good correlation between the number of symptoms and trichloroacetic acid concentration in urine of employees (Table 1). Neither Frant and Westendorp [16] nor we [12] were able to confirm these results.

However, let us use the statistical tables of Ahlmark and Forssman [20] and suppose that under MAC the exposed persons excrete 160 mg. of trichloroacetic acid per liter of urine; let us further suppose that the change in percentage of trichloroacetic acid is independent of trichloroethylene concentration in the air, adopting thus a linear relation (Graph 2).

The Table shows clearly that the MAC standards are too liberal. From Graph 2 we may see that the hygienic limit of 20 mg. of trichloroacetic acid determined by Ahlmark and Forssman [20] involves the concentration of 0.05 mg. of trichloroethylene per liter of air, this being the highest allowable concen-

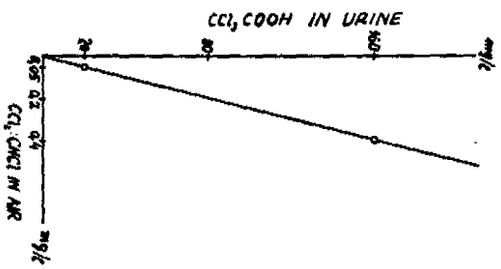

Fig. 2.—Relation between the trichloroethylene content of the air and the trichloroacetic acid content of urine.

tration in the U. S. S. R., according to Bulletin NSP-101.[21]

But we think that the good correlation observed by Ahlmark and Forssman [20] between trichloroacetic acid concentration and the working hazard does not warrant a generalization for purely theoretical reasons.

The acute narcotizing effect is given by the relation where E is the effect and c is the

$$E=F(c)$$

concentration, but in assay of chronic effect on the nervous system, a state typical of trichloroethylene, we must not lose sight of the time effect (t) of the noxious element and of the Haber relation [22]

$$E=f\int_0^{t_1}(c)\,dt$$

The remarkable sleepiness observed by us in most employees can partly be attributed to the trichloroethanol formed during work with trichloroethylene.

In a preceding paper [12] we reported as one of the most characteristic intoxication signs an intolerance toward alcohol. We think that explanation for this effect, described in the case of other industrial poisons (toluene, calcium cyanamide, and carbon monoxide) as well, may be sought in attenuation of the oxidation systems by trichloroethylene itself and its metabolism (e. g., oxidation of chloral hydrate to trichloroacetic acid ¶).

The response to alcohol in persons working with trichloroethylene being similar to that in persons treated with tetraethylthiuramdisulfide, we suggest that here also acetaldehyde evolved from alcohol exerts its influence, probably upon the acetylcholine mechanism. The alcohol-disulfiram (Antabuse) response may be suppressed by atropine administration, and this fact is in favor of the suggested mechanism.# Inhibition of tissue respiration leads to increased trichloroethanol production, the result being increased sleepiness. And we find both these systems, sleepiness and alcohol intolerance, very often side by side. Intolerance to alcohol eventually disappears when work has been discontinued.

Bardoděj, Krivucová, and Pokorný * found also that tetraethylthiuramdisulfide increases intoxication signs in experimental animals after inhalation of trichloroethylene.

Liver damage from trichloroethylene was not observed in our country, perhaps owing to the high purity of the product which observes the standard set by the British Pharmacopoeia. The starting material for making trichloroethylene may be tetrachloroethane or other agents. We agree with Elkins [19] that liver changes reported by other investigators may be due to these other agents.

Trichloroacetic acid in the form of salt is a practically nontoxic substance; the lethal dose (L. D_{50}) for the rat is 3 to 5 gm. per kilogram of body weight.[8] Morrison [23] gives the lethal dose of sodium monochloroacetate for the mouse as 165 mg. per kilogram of body weight. Bardoděj, Krivucová, and Pokorný,† experimenting on dogs, arrived at similar relative values.

The potential capacity of the organism for changing trichloroethylene into trichloroacetic acid seems, therefore, of advantage to the host.

Precise biochemical methods for the evaluation of the systemic effects of trichloroethylene exposure are still lacking. We prefer to maintain systematic atmospheric controls of our industrial plants and to use preventive measures rather than to spend time developing new methods of laboratory research. Any case of chronic intoxication which might occur is entrusted to the care of the neurologists.

PART II

Several of the biological effects of trichloroethylene were discussed in the first part of this communication. With some of the vola

¶ Bardoděj, Z.; Krivucová, M., and Pokorný, F.: An Attempt to Find a Biochemical Explanation of Intolerance to Alcohol in Trichloroethylene Intoxication, Prac. lék. 7:263-267, 1955.

Bardoděj, Z.; Krivucová, M., and Skála, J.: Unpublished data.

* Bardoděj, Z.; Krivucová, M., and Pokorný, F.: An Attempt to Find a Biochemical Explanation of Intolerance to Alcohol in Trichloroethylene Intoxication, Prac. lék. 7:263-267, 1955.

† Bardoděj, Z.; Krivucová, M., and Pokorný, F.: Unpublished data.

tile organic solvents, acute intoxication is characterized by two pathological stages: (1) the direct effect of the noxious element upon nerve tissue (narcosis) and (2) the effect of changes the substance undergoes in the body, accompanied often by liver, kidney, and blood-production damage. With trichloroethylene the first stage is the most striking, namely, the lipid solvent effect upon nervous tissue. Death following trichloroethylene inhalation has often been described, the immediate cause of death being respiratory failure or primary cardiac failure. In acute intoxication psychically abnormal response is observed. In psychopathic persons with hysteric inclination, the acute trichloroethylene intoxication provokes hysterical reactions. Upon recovery only some residual signs of damage to the pyramidal system remain. We had a patient who attempted suicide by trichloroethylene inhalation: she suffered central hemiparesis, which subsided within several days, and after six weeks only a stronger bicipital reflex was to be observed.[24]

In chronic industrial intoxication the effect upon the nervous system is the most important. Borbély [25] describes the incipient stage of chronic trichloroethylene intoxication as a toxic encephalosis, a severer stage as an organic psychic syndrome, and the severest as a toxic Korsakoff psychosis. Next to the damage to the brain cortex, other systems may be affected—the vegetative, pyramidal, and extrapyramidal motor systems, the cerebellar vestibular system, and the peripheral nervous system. Diffuse toxic degeneration of nerve tissue and even patch-like changes resulting from small vessel spasm have been suggested.

Among cardiovascular changes, vasomotor changes of central origin were often reported, especially a low blood pressure. The heart may be damaged by changes in the muscle and conduction disturbances. Several cases of angina pectoris have been reported.

Besides the narcotic effect, a local irritation may be observed of conjunctivae and the respiratory tract through the influence of trichloroethylene vapors; in massive intoxication the result may be lung edema. In several cases the lung edema may have been due to phosgene evolving upon contact of trichloroethylene with hot objects, but we observed lung edema in a person who inhaled only pure trichloroethylene.

Liquid trichloroethylene leaves burn-like marks on the skin.

We think it useless to discuss the controversial opinions about liver and blood damage, as well as the selective effect of trichloroethylene upon the trigeminal nerve, found scattered in the literature; we never observed any of these and consider them isolated, accidental, and interesting rather than typical. Interesting observations, with copious references, were published recently in the *A. M. A. Archives of Industrial Hygiene and Occupational Medicine* by McBirney [26] and by Kleinfeld and Tabershaw.[27]

Our object has been (*a*) to ascertain to what degree the clinical picture of chronic trichloroethylene intoxication is dependent upon the concentrations found in the working atmosphere; (*b*) to evaluate the Fujiwara reaction for trichloroacetic acid in urine and its relation to the degree of damage; (*c*) to follow the course of the intoxication parallel with individual exposure intervals, and (*d*) to find out to what degree the injury after chronic exposure might be reversible. To this purpose we examined 75 persons engaged in work with trichloroethylene, their exposures varying from half a year up to 25 years; they were employed in different plants in our district.‡ Of these 75 persons, 12 worked in dry-cleaning establishments, and 55 were engaged in degreasing metal parts. The atmospheric concentration of trichloroethylene in these plants varied between 0.028 and 3.4 mg. of trichloroethylene per liter of air. We also followed clinically the health of eight persons who were disabled and out of work for some time.

In analyzing the clinical picture of employees working with trichloroethylene, we took special notice, first, of the prenarcotic stage, whose intensity is dependent upon the tri-

‡ References 12 and 28.

chloroethylene concentration in the air, and, second, of the specific toxic effects resulting from exposures of longer duration.

The prenarcotic symptoms oftenest encountered were headache, sleepiness, a drunken feeling, nausea, and tinnitus. Signs of local irritation were cough and lacrimation. At first trichloroethylene acts euphorically, with work being done in a convivial spirit accompanied by song.

Later, signs and symptoms of longer duration were seen and varied with the amount of trichloroethylene absorbed—evidence of damage to the vegetative nervous function of certain organs; some of these signs and symptoms persisted after quitting. They consisted of intolerance to heat and sunlight, hot flushes, perspiration, exaggerated heart beat, respiratory difficulties, reddening of the skin after mechanical or heat insults, intolerance to alcohol, and a strongly positive direct dermographism. Respiratory difficulties and palpitations after imbibing alcoholic drinks, cold hands, and direct dermographism were the commonest signs and symptoms. Examination of the histamine blood level revealed no abnormalities even after alcohol administration.[12]

Vegetative disturbances after alcohol ingestion are most likely due to changes in alcohol metabolism.[25] But as we found the intolerance toward alcohol dependent not only upon the atmospheric concentration of trichloroethylene but also upon the duration of work, and as it persists after quitting the job, we believe the mechanism of this disturbance to be more complex, entailing perhaps damage to the diencephalon.

In addition to damage to the vegetative nervous system, signs and symptoms of damage to the rest of the central nervous system are evident—headache, irritability, emotional lability, loss of psychic control, increased uneasiness, easy fatigability both mental and physical, loss of sleep, fine quick tremor and stronger intention tremor, giddiness, shunning of society, loss of former interests, personality changes, emotional distress with weeping, apathy, depression, loss of memory, and anxiety states. We shall refer to these as the neurasthenic syndrome of exogenous origin and degree.

Some of these signs and symptoms were present in some persons before their exposure to trichloroethylene; these persons suffered the ensuing damage more readily and to a higher degree than persons who were healthy and emotionally stable beforehand. Increased drowsiness was noted in all patients: some fell asleep upon return from work and slept through the whole night. Discontinuance of work, even for one day, caused loss of sleep. Several employees interrupted their leave to get some trichloroethylene, without which they were unable to sleep at all.

The history of almost 50% of the employees absent for an average of one year revealed drug addiction. This fact was verified upon finding trichloroacetic acid in their urine.

Neuropsychic balance was examined by a test for active optical attention according to Chalupa [12]; the influence of trichloroethylene showed itself by oscillations of the attention, which were different from those of normal persons.

Close attention was paid to decreased potency, a very common complaint. To determine whether the gonads were damaged primarily or whether the central nervous system was involved, serial neutral 17-ketosteroid determinations were made, but the decreased values found were not statistically significant. The decreased potency may be attributed to damage to the central nervous system, although increased sleepiness may play a part. A rather large percentage of the women suffered disturbances of the menstrual cycle.

In examining the peripheral nervous system, we found very often perineuritis, especially in the brachial plexus and in the first division of the fifth cranial nerve. Optical nerves were unchanged, but damage to the function of eye muscles was encountered in two patients.

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ing pyramidal symptoms in persons who gave a history of acute trichloroethylene intoxication. Increased axial reflexes were found in several persons but mostly in those above 45 years of age, where the possibility of arteriosclerotic damage to the basal ganglia could not be ruled out.

The above-mentioned neutral 17-ketosteroid determinations served also to insure the production of adrenal *N*-corticoids as normal. The Thorn test was done on all patients after administration of 0.3 mg. of epinephrine (Adrenalin). Pathological findings, e. g., a decrease of peripheral eosinophiles not reaching 50%, were noted in 16% of the persons examined. Following corticotropin (25 mg.) administration, a normal eosinophile level was observed in all persons. Since we regard the Thorn test after the administration of epinephrine significant for the function of the system—brain cortex-hypothalamus-hypophysis-adrenal cortex, abnormal results noted here must be due to damage to either the brain cortex or the hypothalamus. Results of the Thorn test after epinephrine administration were abnormal in five out of nine persons disabled because of chronic trichloroethylene intoxication. But the number of pathological results—16%—was, on the whole, small.

Vyskočil found considerably more abnormal results—59%—in persons working in an atmosphere contaminated with carbon monoxide after examination by the Thorn test following administration of epinephrine. These results were 26% in the case of persons working in hot surroundings and 12% in silicotics.§

The examination of other organs revealed a polycythemia, in which the erythrocyte count was above 5,250.000 in 10% of the patients. This may be explained by a compensatory response of the organism to anoxia rather than to toxic irritation of the bone marrow. However, the hemoglobin, hematocrit, and erythrocyte volume and color concentration in all these cases were normal. Leucocyte and differential counts were normal in every instance.

Current clinical and laboratory tests for the function of the liver, kidney, and gastrointestinal tract failed to reveal any abnormalities (MacLegal thymol turbidity test, Weltmann and Takata-Ara test). But we found that persons with preexisting liver disturbances were very susceptible to the effects of trichloroethylene and developed various symptoms of intoxication, because of which they had to discontinue work with trichloroethylene. Bardoděj and Krivucová ‖ found positive urorosein reaction in the urine of 50% of all employees working with trichloroethylene. The glutathione level was within normal limits.

The examination of the cardiovascular system revealed, besides the vasomotor changes already mentioned, bradycardia (below 60 beats per minute) in 26 patients, especially those with longer working history. This may be due to increase of the vagus tone. The same cause may underlie the origin of observed supraventricular extrasystole. Among persons working with trichloroethylene for a longer time, we found conduction disturbances; in two instances it was the left Tawara branch block, in one a 3:2 Wenckenbach period and shortening of the PQ and WPW. Heart muscle disturbances were found by electrocardiograph examination in three persons.

Very common were complaints of bronchial catarrh and conjunctivitis and of pains in the joints and muscles, receding after a considerable absence from exposure.

Direct correlation of any of these signs and symptoms and trichloroethylene exposure was found only in the prenarcotic signs and symptoms which occurred to a greater degree at higher concentrations (Table 2).

Correlation with duration of exposure gave statistically significant results ($P<0.01$),

§ References 29 and 30; Vyskočil, J.: Endocrine Picture in Acute and Chronic Carbon Monoxide Intoxication, Sborn. lék. **58**:41-52, 1956.

‖ Bardoděj, Z., and Krivucová, M.: Trichloroethylene Hazard in Prague Dry-Cleaning Establishments, Čs. hyg. epid. mikrob. immun. **4**:90-94, 1955.

TABLE 2.—*Comparison Among Workshops of Damage to Health of Employees*

Workshop	Dry Cleaning	Degreasing of Metal Parts		Absent from Work
Trichloroethylene Concentration in Air, Mg./L.	0.16-3.4	0.54-0.83 I.	0.028-0.055 II.	One Year
Persons examined, no.	12	19	36	8
Average age, yr.	42	44	31	48
Duration of exposure, yr.	14	8	1.75	12
Trichloroacetic acid, mg./l.	140	75	32	
Headache	9 75%	5 26%	24 67%	5 62%
Sleepiness	8 66%	11 58%	25 69%	1 12%
Drunken feeling	6 50%	2 10%	10 28%	1 12%
Nausea	6 50%	3 16%	5 14%	0 0
Dizziness and fainting	5 41%	6 31%	8 22%	2 25%
Tinnitus	2 16%	3 16%	6 17%	1 12%
Lacrimation	11 92%	7 37%	12 33%	2 25%
Cough irritation	6 50%	11 58%	12 33%	2 25%
Reddening of skin	8 66%	9 47%	10 28%	2 25%
Intolerance to alcohol	11 92%	12 63%	8 22%	3 37%
Decreased sensitiveness of hands	6 50%	3 16%	2 5%	5 62%
Neuritis	3 25%	7 37%	12 33%	6 75%
Tremors	7 58%	1 5%	3 8%	5 62%
Sexual disturbances	2 20%	7 46%	0 0	4 50%
Menstrual disturbances	1 50%	2 50%	7 27%	.. ..
Giddiness	4 33%	8 42%	8 22%	3 37%
Disturbance of sleep	10 83%	5 26%	8 22%	6 75%
Fatigue	11 92%	9 47%	22 61%	7 87%
Neurasthenic syndrome	3 25%	5 26%	9 25%	1 12%
Severer neurasthenic syndrome with anxiety states	2 16%	1 5%	0 0	5 62%
Bradycardia (below 60 beats/min.)	4 33%	8 42%	6 16%	2 25%
Conduction disturbance (electrocardiograph)	1 8%	3 16%	1 3%	1 12%
Heart muscle disturbance (electrocardiograph)	1 8%	1 5%	1 3%	0 0
Bronchitis	3 25%	8 42%	10 28%	3 37%
Conjunctivitis	7 58%	5 26%	12 33%	1 12%
Histamine substances (mg./100 cc.), arith. mean	2.16	1.98	2.04	2.15
Thorn test in per cent of eosinophile decrease	.. 75%	.. 64%	.. 64%	.. 54%

TABLE 3.—*Dependence of Health Damage Upon Length of Exposure*

Duration of Exposure to Trichloroethylene	One Year and Less	Two Years and Less	Nine Years and Less	Ten Years and More
Persons examined, no.	18	18	19	20
Average age, yr.	32	33	36	40
Trichloroacetic acid, mg./l.	40	35	60	80
Headache	14 78%	10 55%	10 53%	9 45%
Sleepiness	12 67%	12 67%	12 63%	9 45%
Drunken feeling	5 28%	3 17%	7 37%	4 20%
Nausea	1 6%	4 22%	7 37%	2 10%
Dizziness and fainting	1 6%	6 33%	7 37%	7 35%
Tinnitus	2 11%	7 39%	1 5%	4 20%
+ Lacrimation	6 33%	5 28%	10 53%	11 55%
Cough irritation	6 33%	7 39%	8 42%	10 50%
+ Reddening of skin	3 17%	7 39%	9 47%	10 50%
x Intolerance to alcohol	5 28%	3 17%	12 63%	14 70%
+ Decreased sensitiveness of hands	2 11%	2 11%	4 21%	8 40%
Neuritis	4 22%	8 45%	6 31%	10 50%
x Tremors	1 6%	0 0	5 26%	10 50%
Sexual disturbances	1 14%	0 0	3 20%	9 45%
Menstrual disturbances	1 9%	8 47%	2 50%	.. ....
x Giddiness	4 22%	2 11%	7 37%	10 50%
+ Disturbance of sleep	6 33%	4 22%	7 37%	12 60%
Fatigue	11 61%	9 50%	15 79%	14 70%
Neurasthenic syndrome	3 17%	6 33%	6 31%	3 15%
x Severer neurasthenic syndrome with anxiety states	0 0	0 0	1 5%	7 35%
x Bradycardia (below 60 beats/min.)	3 17%	2 11%	7 37%	8 40%
Conduction disturbance (electrocardiograph)	0 0	1 6%	1 5%	4 20%
Heart muscle disturbance (electrocardiograph)	0 0	1 6%	0 0	2 10%
Bronchitis	5 28%	4 22%	6 31%	9 45%
Conjunctivitis	5 28%	6 33%	6 31%	8 40%
Histamine substances (mg./100 cc.), arith. mean	1.96	2.04	2.18	2.0
Thorn test in per cent of eosinophile decrease	64%	67%	66%	64%

Correlation of symptoms marked with + upon length of exposure as calculated with λ^2 reached the significance of $P < 0.05$ and of symptoms marked with x, the significance of $P < 0.01$.

with signs and symptoms of more permanent character—intolerance to alcohol, shivers, giddiness, neurasthenic syndrome with anxiety states, bradycardia, and conduction disturbance in the heart muscle (Table 3). A strikingly severe syndrome was found in eight persons, appearing in one of them after a 3-year exposure and in the rest after an exposure of more than 10 years.

About one year after a patient quits work with trichloroethylene, the symptoms of vasomotor disturbance, bradycardia, and conjunctivitis tend to disappear, while bronchitis and disturbances of the central nervous system and heart muscle conduction continue.

As to the dependence of the amount of excreted trichloroacetic acid upon the degree of injury to the patient, we were unable to find anything definitive. The amount of trichloroacetic acid in the urine only shows the degree of exposure to trichloroethylene vapors within a short time before the examination, and even this relation varies in the same person.

In permanently disabled persons, with the exception of drug addicts, we found almost no trichloroacetic acid in the urine, while signs of intoxication were undoubtedly present.

The results of our investigation show the allowed trichloroethylene concentration to be too high, as upon that threshold trichloroethylene acts toxically. We should advocate setting the MAC at 0.2 mg. per liter. Only in workshops with trichloroethylene concentration around 0.05 mg. per liter were employees free of the more serious symptoms.

PART III

The prevention of trichloroethylene intoxication lies with the engineer and depends largely upon the discipline of the employees. Hermetic sealing of the apparatus and careful manipulation can prevent the escape of trichloroethylene vapors. Trichloroethylene has many excellent properties which make its use in industry desirable, but one must never forget that it is a powerful anesthetic.

Persons working with trichloroethylene should take care not to come into direct contact with it (in the liquid form) and should observe hygienic rules, especially in cleaning the apparatus and in opening it, as these points are the source of most acute accidents.

The protective influence of outdoor activities was found to be statistically significant ($P<0.01$). Sportsmen used to exercise in the open air suffered less damage to their health, as they were able more effectively to get rid of the noxious vapors by exhalation and to aid their elimination by oxidation. A similar protective influence was found in protein-rich food, which proved to be of statistical significance ($P<0.01$).[12]

In seriously affected persons the administration of vitamins of the B group (thiamine, lactoflavin, nicotinamide) and of ascorbic acid was found helpful.

Work with trichloroethylene is unsuitable for persons with any neurologic or cardiac abnormalities, persons psychically unstable, those suffering from hypotension, bronchitis, or undernourishment, alcoholics, pregnant women, and women with menstrual irregularities.

SUMMARY

When proper hygienic rules are observed, trichloroethylene appears less dangerous than other solvents.

Trichloroethylene is above all a nerve poison. The most important signs and symptoms of chronic intoxication are intolerance to alcohol, tremors, giddiness, neurasthenic syndrome with anxiety states, bradycardia, and conduction disturbances in the heart muscle.

We think the highest allowable trichloroethylene concentration in the air (0.4 mg. per liter for Czechoslovakia, 100 or 200 ppm for U. S. A.) too liberal and advocate a lowering to 0.2 mg. per liter in Czechoslovakia, better still to 0.05 mg. per liter.

We think that the finding of 160 mg. of trichloroacetic acid in a liter of urine indicates that the MAC has been exceeded, and that even lower values do not exclude that possibility.

The employees should take care to get sufficient exercise in the open air, as this

aids exhalation of the noxious vapor and supports oxidation. The administration of vitamins of the B group and of ascorbic acid has proved useful. Food rich in proteins helps persons threatened with intoxication.

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Dinitroort

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GORDON S. BATCHE
KENNETH C. WALKE
and
JOSEPH W. ELLIOTT,

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