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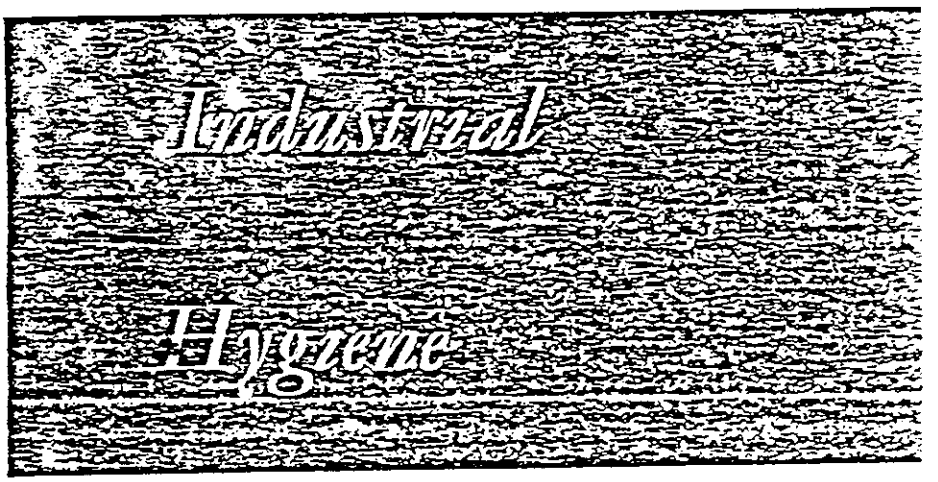

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Conclusion

THERE EXISTS a continuing need to have a coordinated, objective appraisal of radiation hazards to develop a definition satisfactory to health officers in government and industry and to legal authorities. Having defined a "hazard," appropriate controls can be more clearly spelled out on the degree of competency of the supervising personnel.

In the Field of Toxicology

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IN THE BRIEF space allotted to review recent developments in the field of industrial toxicology, those subjects have been selected that appear to be of interest, either because of the unique character of their response or their indications of importance to industrial health. In the vast field from which to choose it is obvious that other selections might have been made equally as well.

New Hazardous Compounds

ACRYLAMIDE, $CH_2=CH-CONH_2$, a chemical intermediate of great potential usefulness for the formation of polymers and copolymers, plasticizers, dispersants and other purposes, has the unusual property of being insidiously neurotoxic at relatively low levels of intake, while at the same time showing unremarkable toxicity from acute doses (oral LD50, 170 mg/kg).[1] Acrylamide is toxicologically remarkable in other ways.

1. It shows practically no species restriction; effective doses for the cat, dog, and rat were essentially the same.

2. Its physiologic effects are produced equally readily by any route, oral, skin or eye.

3. A definite quantity of acrylamide will produce the characteristic central nervous system syndrome of disturbed gait, postural tremors, visual and auditory hallucinations and muscular atrophy, irrespective of the dosage schedule used.

4. There is an anamnestic response, in that following cure, lesser amounts of acrylamide recall the syndrome. Fortunately the effects are reversible, although in severe cases recovery may require years (in man). No threshold limit defining the level for safe exposure has yet been set.

Acrylamide represents an interesting demonstration of our current inability to predict the grave physiologic consequences from chemical structure; the closely related amide, propionamide ($CH_3CH_2CONH_2$), is used as an animal feed supplement. Here, again, is another striking case of the addition of a second double bond in the molecule to form a conjugated system with conference of remarkable toxicity. Another well-known example is the 44-fold greater toxicity of crotonaldehyde compared with its saturated analogue butyraldehyde (Skog, Acta Pharm. Tox. 6, 299, 1950). Less well known, but equally striking is the highly lacrimatory power of conjugated unsaturated nitrocompounds such as 1 nitroisobutylene compared with the unsaturated but not conjugated isomer, 1-nitroisobutyl-2-ene which has no marked lacrimatory powers. The potent irritating capacity of the diisocyanates discussed below are other examples of the effects of conjugated unsaturated compounds. Examples could be multiplied almost endlessly.

As a new group of monomeric substances used in foam rubber, lacquers and for other purposes, the aromatic diisocyanates, especially 2, 4-diisocyanotoluene (TDI), 1, 5-diisocyanonaphthalene, and 1, 4-diisocyanobenzene present interesting toxicologic properties. Although extremely inert in polymeric forms, and possessing a very low oral toxicity 1-8 g./kg.,[2] these aromatic isocyanates, particularly the naphthalene derivative, are exceedingly irritating to the upper respiratory tract, producing histologic changes in animals at 0.09 ppm and death at 1 ppm upon repeated inhalation exposures. Man also responds at exceedingly low concentrations with evidences of allergic sensitivity such as asthma at air levels well below 1 ppm. Peculiarly sensitive individuals may show responses below 0.1 ppm, which is below the odor threshold of toluene diisocyanate for many individuals.

A level of 0.5 ppm of TDI produces throat irritation. The tentative threshold limit has been set for TDI at 0.1 ppm. In our present state of knowledge it is believed that the upper respiratory tract is first involved

following inhalation of low concentrations of the isocyanates, pulmonary edema occurring only at far higher TDI concentrations. All evidence to date indicates no other type of systemic involvement from the isocyanates if the respiratory tract itself is free of involvement. Moisture greatly reduces the toxicity of 1, 4-diisocyanobenzene presumably by hydrolysis and destruction of the unsaturated conjugated system.

Three boron hydrides, diborane, pentaborane and decaborane have received considerable toxicologic and pharmacologic study.[3-6] Used as high-energy fuels these boranes are highly hazardous by all practical routes of entry into the body.

Diborane (B_2H_6), a gas at room temperature (b.p. −92.5C) differs from the others in toxicologic action in possessing no neurotoxic properties presumably because of its ease of hydrolysis; it is however, acutely, subacutely and chronically injurious to the lungs, producing congestion, edema and hemorrhage in higher doses and in the kidneys it leads to the production of tubular casts. The threshold limit of exposure has been tentatively set at 0.1 ppm; this is considerably below its odor threshold of from 2–4 ppm.

Pentaborane (B_5H_9) is the most hazardous of the three boranes. This liquid, (b.p. 58C) whose vapor in a two-hour exposure at 14 ppm results in immediate death of mice, at lower concentrations, produces symptoms of weakness and tremors indicative of central nervous system involvement but without the lung involvement seen with diborane. Cumulative effects are seen with low repeated doses. Skin absorption is a possible contribution to the over-all toxicity. On the basis of hazard from the vapor and its severely toxic effects, a tentative threshold limit has been set for this compound of 0.01 ppm. No medical preventive or therapeutic effective agent for this compound has yet been developed; complete protection is afforded by airline gas-masks or a mask cartridge layered with soda lime, silica gel and activated carbon.[7]

Decaborane ($B_{10}H_{14}$) presents a toxicity picture similar to, but slightly less than that of pentaborane but as it is a solid, it presents less of a hazard than pentaborane; accordingly its tentative threshold limit has been set at 0.05 ppm. The cardiovascular [illegible] reported.[8]

It is recognized that the boranes are but additional examples of nonmetal hydrides such as phosphine, arsine, stibine, hydrogen sulfide, etc., which are characterized by their exquisite toxicity.

Although ozone is by no means a new compound, two factors have been shown to have remarkable effects on modifying its toxicity, exercise and pre-exposure. Exercise during exposure to ozone has been shown by the research work at Occupational Health Field Headquarters, U.S.P.H.S. to enhance markedly the toxic effects of ozone; simultaneous, intermittent exercise during a 6-hour exposure to otherwise non-injurious concentrations of ozone (around 1 ppm by vol.) proved lethal to rats and mice. On the other hand, pre-exposure to the same non-injurious levels of ozone, without exercise, resulted in a rapid development of tolerance to multilethal doses of ozone that persisted for at least four weeks. The tolerance which developed within 24 hours, protected the lungs from the pulmonary edema and hemorrhage common to lethal exposures but did not abolish the characteristic spasmodic breathing or the narcosis.

New Industrial Cancerigens

THERE is a tendency to belittle the carcinogenic potentiality of many substances on the basis that carcinogenicity in animals is no proof for carcinogenicity in man. It would seem a more reasonable view to regard all such compounds at least potentially carcinogenic in man.

Sufficient work on beryllium now seems to have been done in one laboratory (Saranac), at least, by Vorwald, Schepers and Scheel[9] to establish beryllium as a carcinogen in the rat. Inhalation of beryllium sulfate for several months (six) produced eventually what was interpreted as an adenocarcinoma of the lung. The cancer has been successfully transplanted subcutaneously in rats, whence it metastasized to the lung and the lymph nodes of the mediastinum. Inhalation of beryllium phosphor (13% Be) produced in three to six months lesions in the lungs which appeared to be squamous cell carcinoma. The beryllium cancer has not been produced by other workers although it is not rat-strain de-

pendent in the hands of the Saranac workers. Alkaline phosphatase inhibition appears to be the first step in the physiologic process leading to tissue changes. It is believed that the $Be(OH)^+$, a form through which all beryllium compounds pass in the fluids of the body, initiates the reaction. The lack of success of other workers elsewhere to reproduce beryllium cancer is still disturbing, however.

Doll[10] has found that the incidence of lung cancer among 105 English asbestos workers employed more than 20 years was tenfold that in the normal population. Cartier[11] studying over a nine-year period 4000 asbestos miners in Canada, involving 128 cases of asbestosis, 40 of them with autopsies, found six of these have bronchogenic carcinoma. Seven cases of lung cancer were found among asbestos miners with no asbestosis.

With such relatively small numbers of cases one must be extremely cautious in drawing the conclusion of a causal relationship between exposure and the disease. Snegireff and Lombard[12] several years ago pointed out in a study of lung cancer in arsenic plants involving similarly small numbers of cases that cancer deaths in any decade could have by chance been either far less than in the population as a whole or several times more than found in the plant. The question to resolve then in the asbestos exposures, is whether a 10-fold greater incidence of lung cancer is large enough to be significant when dealing with small samples of this sort. Before a final decision is reached it would seem well to wait until a more impressive number of cases has been documented. Moreover it seems to this author that the question of the nature of the asbestos in different localities and the associated minerals such as chromium and nickel, both recognized cancerigens, seem to have been too little considered. Asbestos is a fibrous form of several different species of minerals, a point commonly disregarded.

Hydrocarbon Products of Combustion

CARCINOGENIC hydrocarbons have now been shown to be present among the exhaust products of diesel and gasoline engines,[13] and in the air of English[14] and American cities.[15] These products have been shown furthermore to produce skin tumors in mice. Although these findings were made in c nection with community air pollu studies, diesel and gasoline engines are u in many industrial operations. Efficient innocuous operation of a diesel engine f an atmospheric pollution view has b pointed out as possible, moreover, with costly engine redesign.[13] The fact that man lung cancer has not yet been proven arise from the inhalation of these hydroc bon products should not act as a deterr to an active program to reduce the air c tamination of working areas from t source. Recent figures on lung and bronch cancer from smokers and nonsmokers urban (Liverpool) and rural areas[16] sh definitely an urban "factor." The benz rene content of the air of urban areas w eight to 11 times greater than in the ru areas, a ratio which corresponds with estimated mortality ratio among no smokers in those areas. Although the caus relation seems tenable, it should not considered proven, as a considerable part the evidence rests on the statements of t widows of the deceased as to their smoki habits.

Bladder and Skin Cancer

IT HAS NOW been repeatedly found that amino diphenyl produces carcinoma the urinary bladder of dogs fed this sub stance,[17-19] the last of these confirming r ports being that of Deichmann in 1956. Th cancer was predominantly squamous type and was produced from total dose ranging from 30g (English workers) t 113g, 3 to 10 g/kg (American workers). Th British investigators consider 4-amin diphenyl as a more effective bladder car cinogen than either benzidine or 2-acety aminofluorene, and at least as potent a beta naphthylamine.

A resurvey of the British chemical dye industry[20] produced statistical evidence tha bladder tumors are associated with the manufacture of the dyes auramine or magenta, (aminodiphenyl and aminotriphenylmethane dyes (but do not necessarily arise from contact with the finished dyes themselves. Aniline, however, has been definitely excluded as a causative agent in bladder tumors, at least in the British chemical industry over the years 1910-1952.

Straight-run distillates[21] and higher boil-

ing point fractions of catalytically cracked petroleum[23] may contain numerous carcinogenic hydrocarbons. A relationship between exposure to these substances and high incidence of occupational skin diseases other than cancer has been reported[23] and tests in animals with cutting oils have implicated them as possible carcinogenic agents. More recently cutting oils with a sulfonated mineral-oil base have been connected definitely with squamous cell carcinoma of the skin among Canadian metal cutters.[24] Six cases of skin cancer and one case of papilloma have been reported among workers with an average exposure period of about 20 years. Although most of the lesions appeared on the forearms, one case involved the scrotum of a worker on whom oil splashed continually in the region of his lower abdomen, giving a clear definition to the relation between exposure and response from this type of oil. On the other hand, no skin cancer or precancerous manifestations have appeared to date among a group of 180 shale-oil workers in this country studied over a period of the past six years.[25] The group will remain under continued observation, however.

Toxic Thermal Decomposition Products

THE TOXICITY of the degradation products of a large number and variety of plastics, synthetic hydraulic and lubricating fluids and fire extinguishants has been determined chiefly by Treon and associates.[20] The importance of the studies is the finding that the over-all toxicity of the thermally degraded products from each substance was greater by a large factor than the substances from which they originated. The substances studied thus far include Teflon, Kel-F, Fluorolube FS, (all fluoro or fluorochloro-organic polymers), silicones, Gafite, (a chlorinated methacrylate), a paraffinic hydrocarbon lubricating oil, Skydrol, Pydraul F-9, Arochlor 1242, tricresyl phosphate, adipate and sebacate esters and Freon F13B1. In a few instances the toxic factors have been partly identified. As might be expected, the amount, nature and toxicity of the products was dependent upon the temperature of decomposition; in general, greater toxicity was experienced with increasing decomposition temperatures until a maximum was reached at a temperature characteristic of the substance. Temperatures above 500°F generally produced the more important amounts of toxic products from most polymers. The hazards of the decomposition products of the synthetic lubricants and hydraulic fluids are no greater than those from the common lubricating oils; a man would not stay voluntarily in the presence of significant concentrations of these products. Another interesting finding was a marked decrease in toxicity of the thermal decomposition products of Freon F13B1 in the presence of moisture. The mechanism by which this is brought about is being studied.

Trichloroethylene Exposure Problem

THERE is probably no industrial solvent on which there is currently more discussion on the proper level for worker exposure than trichloroethylene. Some indication of the lack of agreement may be seen in the widely different threshold limit values in use in America, (200 ppm); England, ICI (400 ppm); Russia (9 ppm); Italy, Parmegiani (100 ppm). Ahlmark and Friberg in Sweden, on the basis of trichloroacetic acid excretion values would prefer an average daily exposure to trichloroethylene of no more than 30 ppm.[27] Several possible reasons for these widely dissimilar values come to mind.

1. Trichloroethylene may contain appreciable and differing quantities of highly toxic impurities.
2. Differing methods used for sampling and analysis for trichloroethylene.
3. Differing means of appraising effects of exposure to trichloroethylene.
4. National idiosyncracies of dietary habits, metabolism, differing genetic origin and worker age groups.

The problem has importance that transcends that of the proper level for trichloroethylene; it involves also the more general question whether safe levels set for one country are appropriate for another in all instances. To date it is not possible to decide this definitely because, with the exception of Russia, most threshold limit values in use in foreign countries have been taken from values used in the United States. Only recently has a beginning been made in developing values in other countries. Because of the general importance of the question, efforts were made to elicit possible causes of

the difference from a number of foreign investigators familiar with trichloroethylene exposures.

The consensus of the foreign investigators, Ahlmark (Sweden), Truhaut (France), Grandjean (Switzerland) and Soucek (Czechoslovakia) in answer to the above four questions, was that neither impurities in the trichloroethylene nor faults in sampling and analysis of the air are believed to account for the differences. They believe rather that their more thorough medical evaluation, especially neurologic examination, tend to account for their appraisal of trichloroethylene as a more severe hazard to health than considered elsewhere. Answers to the more difficult fourth question of the role of national idiosyncracies were either not forthcoming or were admitted not to have been studied. The question may have an important bearing on the problem, however. Evidences of geography or national differences affecting metabolism of an industrial agent have been obtained from a comparison of vanadium ore workers in Peru and in America.[28]

Measurable changes in fingernail cystine occurred in Peruvian workers at urinary levels above 10μg/l wherens levels greater than 30μg/l were required before changes of similar magnitude were found among U. S. vanadium workers. In defense of the U. S. position of 200 ppm threshold limit for trichloroethylene may be cited the unbelievably low air values obtained by the European workers in the area of trichloroethylene degreasers (Grandjean),[29] the use of trichloroacetic acid as a means of evaluating safe exposure levels (Ahlmark)[27] and the lack of objective evidence in the U. S. of injury among trichloroethylene workers chronically exposed over a period of many years. Further exploration, both medical and toxicologic is needed to clarify this important question.

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