THE TOXICITY OF CERTAIN BENZENE DERIVATIVES AND RELATED COMPOUNDS*

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INTRODUCTION

THE title of this paper may suggest a very wide range of compounds, about the toxicity of some of which we have considerable information but about that of others we know little or nothing. I was recently appealed to by an insurance company to outline a program for safe handling of a compound that I did not know was used in industry and about the toxicity of which nothing has been published so far as I know.

However, though the derivatives of benzene are legion, yet they group themselves into certain main classes, about certain members of which we have information. In most cases members of a class act on the system in a similar manner and differences in action are differences of degree rather than of kind. There are exceptions to this general rule, however, some of which will be pointed out later.

GENERAL CONDITIONS

Benzene, C_6H_6, is the simplest compound of all, and the benzene ring is the basis on which all the others are formed. The so-called homologues of benzene are toluene, $C_6H_5 \cdot CH_3$, and xylene, $C_6H_4 \cdot (CH_3)_2$, in which one or two methyl radicals replace one or two hydrogens (1).

The most important benzene derivatives industrially and toxicologically are the nitro, amino, diamino, and chlor compounds of benzene and toluene. Danger to health from these compounds depends not only on their chemical structure but also largely on their physical state and the method of handling them. Those compounds responsible for the greatest amount of industrial sickness are not necessarily the most toxic.

Homologues of Benzene

Considering first the homologues of benzene, toluene and xylene, we find somewhat conflicting reports. Selma Meyer (2) states that regardless of which poison is acting, whether benzene, toluene, xylene, naphthalene, aromatic nitro compounds, etc., the lymphocytes are increased in the blood stream and the neutrophils are forced back or repressed. American findings do not agree with this. Neither Greenburg (3) nor we (4) have found toluene or xylene presenting any characteristic blood picture in experimental animals. Greenburg found that with continuous exposures for up to seven days, high concentra-

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tions of toluene killed all exposed animals in forty-eight to seventy-two hours with narcosis. Animals surviving lower concentrations showed evidences of narcosis, irritation or depression, with irritability. Our own tests with four-hour exposures over longer periods showed evidences of lung inflammation and of toxic degeneration in internal organs. We both found toluene to be less toxic than benzene, and the National Safety Council recommended it as a substitute for benzene where possible (3). In addition to being less toxic, it is less volatile and is less likely to exist in a plant as vapor of toxic concentration. Xylene we have found also to be quite toxic, but again it is even less volatile than toluene and therefore less hazardous. Neither of these two substances seems to be readily absorbed through the skin in toxic amounts and I know of no case of poisoning from skin absorption due to them.

Nitro and Amino Group Compounds

Nitro and amino groups, aromatics, in general produce much the same clinical pictures, differing in some details and with a few striking exceptions. The latter in general are simple blood poisons, while the former in addition exert a direct action on the central nervous system. Floret (5) says that all aromatic and aliphatic compounds are fat solvents and therefore particularly apt to affect the central nervous system.

In light cases of poisoning from nitro or amino compounds there is flushing of the face, with a sense of fulness and throbbing pain in the head, burning sensation in the throat, and a feeling of tightness in the chest. More marked cases of poisoning develop violent throbbing headache, dizziness, roaring in the ears, and visual disturbances. With still more severe poisoning the face becomes livid, the lips and tongue blue, the knees weak, and the gait staggering. The blue color of the face may persist for several days. In extreme cases cyanosis increases, muscular tremors develop, there is extreme weakness, cold skin, nausea and vomiting, abdominal cramps, quick, shallow respiration, lowered blood pressure, and late unconsciousness. Coma develops, the respirations become progressively slower and shallower, involuntary urination and defecation may occur, and convulsions usually come on just before death. Not infrequently attacks are delayed, coma coming on even hours after cessation of exposure.

The blood picture is characteristic, with reduction in the red cell count and the hemoglobin, poikilocytosis, anisocytosis, and some fragmentation of red cells with polychromatophilia. The blood becomes chocolate colored owing to the development of methemoglobin, the spectroscope showing absorption bands between those of pure methemoglobin and oxyhemoglobin. Evidences of blood regeneration are seen after a few days in non-fatal cases, with the appearance of stippled cells and nucleated red cells. There is an early polymorphocytosis followed later by a relative lymphocytosis. In slow poisoning from continued low exposures there may be an increase in the red cell count. The urine becomes brown, port wine colored, or smoky red, and shows bile and blood pigments, methemoglobin or hemoglobin. At times albuminuria

occurs and the urine may reduce Fehling's solution. For most of this group the skin is the most important entry port.

Amino Compounds

While the amino compounds as a class produce a deeper cyanosis than do the nitro compounds, yet with them, poisoning is less serious and recovery usually results in a few days if exposure is not continued. There are exceptions to this, however. They are all very readily absorbed through the skin as well as through the lungs.

Aniline poisoning is first manifested as an intense cyanosis, the victims of poisoning being referred to as "blue boys." In an aniline plant visited during the war, cases of poisoning occurred daily and blue boys were a common sight. Following cyanosis there develop headache, dizziness, dysphagia, nausea, vomiting, weakness, restlessness, palpitation, and irregular slow respirations with rapid feeble heart action. Pupils are contracted but respond to light. Temperature is subnormal. There is an aniline odor on the breath and to the sweat. The urine is dark in color owing to the presence of hemoglobin. In severe cases there may be a loss of sphincter controls and also pulmonary edema. More cases and more severe poisonings occur in hot weather. Workers may develop a degree of tolerance but the cyanosis may persist. Continued exposure may result in headaches, irritability, poor appetite, neurasthenia, visual disturbances and itching of the eyes which may lead to injury and ulceration of the cornea from rubbing. There is anemia, with decreased hemoglobin. Long-continued exposure is said to produce bladder tumors which may become malignant.

The average lethal dose is 25 gm.; 0.4 to 0.6 mg. per liter of air may be borne without much harm for one-half to one hour but 0.1 to 0.25 mg. per liter for several hours produces slight symptoms (6). Tests made by Lazard (7), in 1920, in the aniline house of a plant while reducers were being discharged, gave the following amounts in milligrams per liter of air: 0.5, 1.01, 1.18, 2.43, and 3.4—all but the first one well above the toxic concentrations. Men were exposed to these concentrations for periods of from twenty to forty minutes. One workman at the plant developed cyanosis from wearing an old pair of gloves found lying in a pool of aniline water on a drumhead. Changes in design of apparatus and method relieved this condition and reduced the number of poisonings in this department almost to the vanishing point; later, however, the plant started to develop the production of synthetic indigo, and new cases began to appear in men discharging the phenylglycine driers, as the finely powdered phenylglycine carried more or less absorbed aniline. Here the poisoning was due to dust inhalation. Two tests taken by Lazard, in the indigo house while the vacuum driers were being emptied, showed 0.7 and 1.7 mg. of aniline per liter of air.

Toluidines produce the same symptoms as does aniline, with less cyanosis but more strangury and hemoglobinuria. They produce subnormal temperature and anemia. Exposure occurs from splashes from centrifuges and whizzers.

Beta-naphthylamine produces cyanosis and also frequent urination as a result of irritation due to overacid urine.

Diamines

The diamines may be decidedly toxic. Phenylenediamines are used as dye intermediates in dyeing hair and furs. They have been responsible for a number of cases of poisoning from hair dyes and from cheap dyed furs. Symptoms produced are dermatitis, sleeplessness, dizziness, and weakness; and epileptiform convulsions, coma, and death may result. The reaction may develop very suddenly and be of anaphylactic type. Some writers have insisted that it was a true anaphylaxis, and Curschmann has suggested calcium therapy with the inhalation of sprayed solutions of calcium salts. Most writers, however, now attribute the poisoning to quinone intermediates resulting from incomplete oxidation, and state that care to secure complete oxidation and careful, thorough washing of dyed furs will prevent the trouble from developing. Phenylenediamine should never be used in hair dyes.

Tolylenediamine is a blood poison, producing destruction of red cells, methemoglobin, and toxic jaundice with liver degeneration, but is less toxic than the phenyl salt.

ANIMAL EXPERIMENTS

At various times in the past few years our laboratory has been called upon to determine the toxicity of a number of benzene derivatives and allied substances, more or less complex, about whose effects on the system there was little or no information available in the literature. Many of these preparations were for use in the rubber industry as accelerators or retarders. Most of these tests have been assembled for comparative purposes and are here presented in the hope that they may be of interest and of help to others called upon to use these materials or to make similar tests.

In many cases all that was desired by those requesting information was the determination of the minimum lethal dose, as an indication of the possibility of accidental acute poisoning. With others the effects of repeated sublethal doses were studied.

All experimental work was done with small animals, it being the custom in our laboratory to use at least two types of animal, often three, for such work. The animals of choice, for convenience in handling, are white rats, guinea-pigs, and rabbits. Dosages are always given as grams per kilo of body weight of the animal at the time of administration. It is customary to interpret the results of such tests in terms of grams per kilo of body weight of man, but we always give such interpretation with considerable reserve, and feel that at best it indicates an approximation to the range of toxicity for man, rather than an actual measurement of it. When used for comparison of the toxicity of different compounds, however, we feel that such tests are a very fair indication of relative harmfulness.

When death occurs within a comparatively few hours from a single dose of a chemical, we rarely find microscopic evidence of toxic organ degeneration, and in these cases we report only dose, time of death, symptoms, and

gross changes noted at autopsy. When animals survive more than twenty-four hours, in addition to gross changes we always look for histologic changes in internal organs, especially the liver, kidney and spleen, and other organs as indicated. When animals survive a week or more, we usually include urine and often blood findings in the reports.

With most of the tests here reported on for minimum lethal dose determinations, no microscopic findings are included. The tests to be reported were made as parts of six different investigations on materials supplied by three different industrial firms. Firm names and trade names of chemicals or compounds are purposely omitted, but empirical and line structural formulas are given when known. In some instances, however, there are differences of opinion as to the structural formula of the compounds reported upon. When materials to be tested were water soluble, they were fed by pipette in watery solution. When not water soluble, if soluble in dilute acid they were fed as hydrochlorides with as little as possible excess acid. Liquids not mixable with water were fed as a starch paste. Solids insoluble in water or dilute acid were fed as a paste in olive oil or water. In all cases, animals being dosed were held in the hand of the operator and it was made sure by personal observation that all the material was actually swallowed. Except as noted, all materials were of the technical grade of purity.

Guanidine and Guanidine Derivatives

Guanidine, CH_5N_3 or $(NH_2)_2 \cdot C{:}NH$, is not in itself a benzene derivative but it enters into compounds that are. The minimum fatal dose for a pure sample of this substance was found to be 0.3 gm. per kilo when dissolved in a weak acid solution and fed as a hydrochloride. With this dose, death occurred in from three to twelve hours, preceded by twitchings, convulsions, collapse, and gasping inspirations.

Diphenylguanidine, $C_{13}H_{13}N_3$ or $(C_6H_5NH)_2 \cdot C{:}NH$, with two substituted phenyl radicals, also fed as a hydrochloride, killed in from one to three hours in a dose of 0.25 gm. per kilo, with the same train of symptoms.

Triphenylguanidine, $C_{19}H_{17}N_3$ or $(C_6H_5NH)_2 \cdot C{:}NC_6H_5$, with three phenyl radicals, fed as a paste in 0.1 per cent. hydrochloric acid, as it would not go completely into solution, killed in from three to four hours in a dose of 0.35 gm. per kilo; death was preceded by violent trembling, convulsions, gasping, violent chewing motions, and characteristic rolling over, always in the same direction.

The addition of the phenyl radicals to the guanidine molecule definitely increased toxicity. The apparent lessening of toxicity of the tri over the di product was no doubt due to its lessened solubility; even though it required a larger dose to kill, the prelethal symptoms were more violent.

Diorthotolylguanidine, $C_{15}H_{17}N_3$ or $(C_6H_4CH_3NH)_2 \cdot C{:}NH$, killed in forty-five minutes in a dose of 0.12 gm. per kilo; this also was fed as a hydrochloride in solution. Prostration developed rapidly, with twitchings, irregular shallow breathing, gasping, and cyanosis. Larger doses killed in twelve minutes. Here the tolyl radical produced a marked increase in toxicity. That the tolyl radical does not always insure toxicity is seen in the case of diorthotolylthioures, $C_{15}H_{16}N_2S$

or $(C_6H_4CH_3NH)_2 \cdot CS$, in which it is combined with a harmless sulphur compound. Here no symptoms were observed with a dose of 4 gm. per kilo, though the same tendency, in a slight degree, was seen to the development of lung hemorrhage as was observed in almost all of these series. Dosages were not increased beyond 4 gm. per kilo because the corresponding dose for man would be tremendous and it was extremely difficult to feed larger doses to animals.

With the materials of the guanidine series there was a very sharp line between the fatal dose killing in at most a few hours and the dose from which there was apparent complete recovery. No animal that survived overnight died. The behavior of the animals dying from these materials strongly suggested cyanide poisoning, as did the behavior of one factory employee whose death was possibly the result of an accidental overdose of one of the guanidine derivatives.

A series of animals were fed sublethal doses daily of diorthotolylguanidine for up to twelve days. In these animals traces of a substance reducing Fehling's solution appeared in the urine after each feeding, but did not persist overnight. They all developed mild albuminuria but no casts, and postmortem examination showed early but not marked liver and kidney changes. There was evidently no rapid cumulative effect.

Aniline and Aniline Derivatives and Compounds

A number of aniline derivatives were tested and compared with aniline. Aniline itself, C_6H_7N or $C_6H_5NH_2$, reported in the literature as fatal for man in doses of 0.35 to 1.43 gm. per kilo (as a pure preparation), killed guinea-pigs in doses of 1.75 gm. per kilo when fed as pure aniline

Thiocarbanilide, $C_{13}H_{12}N_2S$ or $(C_6H_5NH)_2 \cdot CS$, a thiourea derivative, proved nonfatal in doses of 4 gm. per kilo, fed as a paste in olive oil, though the animals seemed weak and depressed and petechiae were seen in the lungs. Lack of solubility lessened toxicity, as did also the entrance of sulphur.

Methylenedianilide, $C_{13}H_{14}N_2$ or $(C_6H_5NH)_2 \cdot CH_2$, was also nonfatal in doses of 4 gm. per kilo, and no symptoms were observed. This material also was fed as a paste in olive oil, and insolubility probably was the reason for nontoxicity.

Paranitrosodimethylanilide, $C_8H_{12}N_2O$ or $NO \cdot C_6H_4N(CH_3)_2$, a nitroso compound fed as a paste in water, proved to be twice as toxic as aniline, even though not easily dissolved. It was fatal in doses of 0.65 gm. per kilo in from twelve to forty-eight hours, death being preceded by prostration and convulsions, and red staining of the urine.

A series of condensation products containing aniline gave interesting results. Formaniline $(C_7H_7N)_x$ or $(C_6H_4N:CH_2)_x$, a combination of two definitely toxic substances but itself soluble with difficulty was not fatal in doses of 4 gm. per kilo.

A trade compound, a condensation product of aniline, acetaldehyde and formaldehyde, and another made from aniline, acetaldehyde and carbon disulphide, also very slightly soluble and fed as olive oil pastes, were not fatal in doses of 4 gm. per kilo.

Paratoluidine, C_7H_9N or $CH_3 \cdot C_6H_4 \cdot$

NH_3, (pure preparation) fed as a paste in water, killed in a dose of 1.1 gm. per kilo. This was surprising as Hamilton (1) quotes Gibbs and Hare as giving 0.1 gm. per kilo as fatal for animals.

Anhydroformaldehyde-paratoluidine, $(C_8H_9N)_x$ or $(CH_2 \cdot C_6H_4N:CH_2)_x$, fed as a paste in 0.1 per cent. hydrochloric acid, was less toxic, the fatal dose being 2 gm. per kilo, killing in twelve hours; death was preceded by trembling and kicking, but no general convulsions occurred. This is the toluidine analogue of formaniline reported previously, and the substitution of toluidine for aniline markedly increases toxicity.

A condensation product of aniline, paratoluidine, butyraldehyde and carbon bisulphide was more toxic than anhydroformaldehyde-paratoluidine, but not so toxic as paratoluidine. It killed in doses of 1.7 gm. per kilo in from two to six hours; death was preceded by prostration and collapse but there were no convulsions. This was an oily fluid with presumably a smaller molecule than anhydroformaldehyde-paratoluidine, and size of molecule seems to bear some inverse ratio to toxicity.

Diphenyl and Diphenyl Derivatives

Technical grade diphenyl, $C_{12}H_{10}$ or $C_6H_5 \cdot C_6H_5$, prepared by passing benzene vapor through a red-hot iron tube, little if at all soluble in water but readily soluble in alcohol and ether (8), was not toxic in doses of 4 gm. per kilo.

Two chlorodiphenyl preparations, $C_{12}H_9Cl$ or $C_6H_5 \cdot C_6H_4Cl$, were tested and both proved slightly toxic; the 2-chloro compound killed in from twenty to forty hours in a dose of 2.5 gm. per kilo, with mild convulsions, and the 4-chloro compound killed in forty hours in a dose of 3.5 gm. per kilo, with no convulsions. Both were fed in pastes as they were apparently insoluble. Here the position of the chlorine atom seemed to govern the degree of toxicity.

Two polychlorodiphenyls, the definite compositions of which were undecided, proved nontoxic in doses of 4 gm. per kilo. They were also fed in pastes, and were composed of even larger molecules than the monochloro compounds.

A 4-nitrodiphenyl, $C_{12}H_9NO_2$ or $C_6H_5 \cdot C_6H_4NO_2$, in spite of its nitration was not fatal in doses of 4 gm. per kilo, owing probably to its insolubility.

Nitrobenzene

Nitrobenzene, $C_6H_5 \cdot NO_2$, decidedly toxic as a vapor and by skin absorption, the latter due to its solubility in fat, was less toxic (using a pure preparation) than we had anticipated, when fed in a starch paste, the fatal dose being 1 gm. per kilo for animals.

Phenylnaphthylamines

Both alpha and beta naphthylamine, $C_{10}H_9N$ or $C_{10}H_7 \cdot NH_2$, are decidedly toxic but their phenylated compounds, $C_{16}H_{13}N$ or $C_{10}H_7 \cdot NH \cdot C_6H_5$, proved very little toxic. The alpha compound fed as a paste required 4 gm. per kilo to kill in three days, while the same dose of the beta compound was not fatal. Here the alpha position proved the more toxic.

Tolylenediamines

We have stated above that tolylenediamine is a blood poison, producing

destruction of red cells, methemoglobin, toxic jaundice, and liver degeneration. It has, however, been suggested as a substitute for the phenylenediamines as a hair dye, on the ground of its much lower toxicity.

Tests were made with both the para and the meta compounds, $C_7H_{10}N_2$ or $CH_3 \cdot C_6H_3 \cdot (NH_2)_2$, the former as an ingredient of a hair dye and the latter as a rubber chemical.

Metatolylenediamine was fed as a hydrochloride in water. The fatal dose was 3 gm. per kilo; however, 0.7 gm. per kilo daily for nineteen days was fatal to a guinea-pig, and 0.6 gm. per kilo daily for five days killed a rabbit. In animals surviving several days there was evident definite fatty degeneration and also renal degeneration. The body fluids were stained with the material and chemical tests showed that some of it was excreted unchanged in the urine. When combined with unvulcanised rubber it was not extracted from the rubber when that was applied to the skin and held there as a poultice for several hours, though it was very slowly extracted by a buffered watery solution ranging between a hydrogen ion concentration of 3 and of 7. The toxicity tests for this product seem to agree fairly well with those previously reported by Stadelmann (9) though he did not report in grams per kilo.

Paratolylenediamine was tested as an ingredient of a hair dye. For testing, this material was used in solutions of three different strengths as recommended for dyeing, containing amounts of the active ingredients ranging from 2 to 39.6 per cent., depending on the depth of color desired. The minimum fatal dose by mouth was found to be about 3.6 gm. of the pure substance per kilo—not very toxic. We found the material toxic to this extent by mouth and by subcutaneous injection, but could see no evidence of absorption through the unbroken skin. When used as a dye it is oxidised with hydrogen peroxide to bring out the full depth of color.

General Pathology of Entire Series

The one outstanding pathologic lesion seen in animals of the series poisoned with the various benzene derivatives was a tendency to extravasation of blood in the lungs, whether the animal died from the drug or was killed for study. This varied from scattered minute petechiae to larger ecchymoses or even massive lobular or lobar hemorrhage, the severity of the lesion usually paralleling the severity of the poisoning. In order to avoid agonal congestions seen in gassed animals, the animals were killed by rapid severing of the spinal cord. By this method we practically never found such hemorrhagic lung conditions in normal animals. In animals surviving several days these lesions were found to be in the process of absorption and they did not seem to lead to pneumonic conditions, though we should surmise that repeated lesions of this type would lower the resistance of the lung to infection. Similar lung lesions were found post-mortem in a fatally poisoned worker who may have been a victim of the acute effects of one of the guanidine derivatives.

In animals which survived several days and then died or were killed for study, there was usually seen some evidence of early toxic liver and kidney degeneration. No animals of this series survived long enough or had sufficient repeated doses to develop marked blood changes.

With most of these preparations the toxicity was rather low. There is very little danger of accidental poisoning in industry with any material having a minimum lethal dose of over 0.25 gm. per kilo, or 17.5 gm. for a man weighing 70 kilos. With limits under that point but over 0.1 gm. per kilo, there is little danger in handling the preparations if their possible toxicity is realised and reasonable precautions are taken as to dust and fume removal and personal cleanliness. It must be borne in mind, however, that personal idiosyncrasy may make exceptions to this rule, and also that fat soluble or lipoid soluble materials, if water insoluble, may poison by skin absorption in doses not toxic by mouth.

It must be emphasized that the toxicities here reported refer only to administration of solids or liquids by mouth. As previously stated, fat or lipoid soluble substances may be decidedly more toxic by skin absorption than by oral ingestion; also it must be borne in mind that the same may be true of vapor inhalation. Therefore these results do not necessarily represent the hazards of industrial exposure to vapors or to skin absorption.

TABLE 1.—SUMMARY OF TOXICITIES REPORTED

Grams per kilo of body weight for small animals (guinea-pigs and rabbits)

Guanidine and Guanidine Derivatives	
Guanidine	0.20
Diphenylguanidine	0.25
Triphenylguanidine	0.25
Diorthotolylguanidine	0.12
Diorthotolylthiourea	4.+
Aniline and Aniline Derivatives and Compounds	
Nitrobenzene by mouth	1.00
Aniline	1.75
Thiocarbanilide	4.+
Methylenedianilide	4.+
Paranitrosodimethylaniline	0.65
Paratoluidine	1.10
Condensation Products	
Formanilide	4.+
Anhydroformaldehyde-paratoluidine	2.0
Formaldehyde, Aniline, Acetaldehyde	4.+
Aniline, Acetaldehyde, Carbon bisulphide	4.+
Aniline, Paratoluidine, Butyraldehyde, Carbon bisulphide	1.7
Diphenyl and Diphenyl Derivatives	
Diphenyl	4.+
2-chlorodiphenyl	2.5
4-chlorodiphenyl	3.5
Polychlorodiphenyl, A	4.+
Polychlorodiphenyl, B	4.+
Phenylnaphthylamines	
Phenyl-alpha-naphthylamine	4.0
Phenyl-beta-naphthylamine	4.+
Tolylenediamines	
Metatolylenediamine	3.0
Paratolylenediamine	3.6

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