TOXICOLOGY OF HERBICIDES

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I. INTRODUCTION

In their endeavours to raise productivity, agriculturists have made use of chemicals to a steadily increasing extent. For the purpose of controlling injurious insects, fungi, weeds, *etc.*, a great number of pesticides has been developed, among which the insecticides, especially the organophosphate cholinesterase inhibitors, have attracted considerable toxicological interest. Relatively little has been written about herbicides, *i.e.*, compounds which have been found useful for weed control. Many of the toxicological data underlying assessments of the risk involved by using them in practice originate from confidential, non-published reports placed at the disposal of the authorities concerned. Such data have not been included in the present survey. Of a number of compounds, the toxicology of which has been elucidated in relation to their use for purposes other than as herbicides, only a brief account will be given with references to relevant literature.

Regarding the practical use of herbicides, reference is made to handbook literature (70, 80, 119, 120). Weedkillers usually are classified into two main groups, selective and non-selective. The selective substances can be used on crops without damaging the cultivated plants, whereas the non-selective types kill all vegetation. Substances of the latter group may therefore be used also for destroying potato haulm and for desiccation of green parts of plants which may unduly delay harvesting, in which case they are often called desiccants or defoliants. The herbicides are grouped, according to their mode of distribution in

the weeds, into contact herbicides, which are active only at the site of application, translocated herbicides, which are distributed throughout the whole plant from exposed parts of foliage or roots, and residual herbicides, which are spread on or in the soil and are effective mainly against germinating seeds.

For the present survey of the toxicology of the herbicides, a classification according to chemical configuration has been chosen. Inasmuch as common names, abbreviations, and registered trade marks ® are used indiscriminately in the literature, we have, as far as possible, included the common names recommended for pesticides by the British Standards Institution, marked (*), names approved by the British Weed Control Council (†), and those approved by the Weed Society of America (‡).

II. INORGANIC HERBICIDES

Prior to the Second World War, mainly inorganic compounds were used for chemical weed control. However, as their actions are not very selective and they are often very persistent in the soil, so that damage to cultivated crops has been difficult to avoid, they have been replaced by organic compounds to a steadily increasing extent. Yet, various familiar inorganic compounds are still used as herbicides, *e.g.*, calcium cyanamide, cupric sulphate, ferrous sulphate, mercurous chloride, potassium cyanate, and sodium tetraborate (borax). The toxicological data on these are well known from the handbook literature. The same is true of arsenites, sodium chlorate, and sulphuric acid, but these compounds will nevertheless by described briefly, because their use as herbicides has introduced special problems of toxicity.

A. Arsenites

Arsenites are used as non-selective herbicides, especially for destruction of potato haulm, as aqueous solutions of potassium-ortho-arsenite ($K_3As_3O_3$) and sodium ortho-arsenite ($Na_3As_3O_3$). The preparations may also contain meta-arsenite and pyro-arsenite alkali salts.

In rats, the LD50 for alkali arsenites has been found to be 70 mg/kg when administered by mouth and 150 mg/kg when applied dermally (32). In domestic animals (40) and man (105) the toxicity is considerably higher, fatalities having occurred in the horse, cow, and man after oral ingestion of 2 to 10 mg/kg. The solubility, preparation, and purity have a considerable influence on the toxicity of arsenic compounds (48); the toxic properties, actions on the animal organism, manifestations of poisoning, *etc.*, have been excellently summarized recently (108).

The use of arsenites as weedkillers has occasioned an extensive series of acute, often fatal cases of poisoning in domestic animals, especially cattle, which have eaten contaminated crops or residues of sprays (40). Concentrations toxic to man have been found in milk from cows fed on crops contaminated by arsenites (61). Cases of direct human poisoning have also been observed. An instance has been described where one woman died and four others fell ill after drinking water from a reservoir which had been contaminated through a leaking pump valve in the

tank of an apparatus for spraying arsenite weedkiller. The drinking-water contained 180 p.p.m. (parts per million) of As (7, 8). This instance of poisoning in Great Britain resulted in a voluntary agreement between industry and the authorities for discontinuing the use of arsenite herbicides (32).

B. Sodium chlorate

Sodium chlorate and other chlorates are extensively used for killing all vegetation of farmyards, railway tracks, roadsides, *etc.*, as well as for destruction of potato haulm. Chlorates possess no particularly great acute toxicity, the LD50 for sodium chlorate administered by mouth to rats having been stated to be 1200 mg/kg (32). Nevertheless, oral ingestion of both sodium chlorate and potassium chlorate, used in oral hygiene, has caused numerous cases of poisoning in man (21, 33, 105). In domestic animals, too, cases of acute poisoning have been observed after oral ingestion of chlorates (40). The mechanism of the poisoning—methemoglobin production and its consequences—has been well studied (21, 33, 106).

A special problem is that of the high inflammability of sodium chlorate. This can be reduced in commercial preparations by admixture with calcium chloride or sodium chloride, but after dissolution in water and spraying, dried residues may become ignited. In Denmark, a tractor driver whose clothes had become impregnated with sodium chlorate during spraying, died of severe burns after they were ignited by a red-hot exhaust pipe.

C. Sulphuric acid

Sulphuric acid, which in certain countries, *e.g.*, Great Britain, is commonly used for potato haulm destruction, is often applied in high concentrations. Accidents with severe skin burns and eye burns may therefore occur (32). Inhalation of sulphuric acid may also exert a toxic effect, as indicated by studies on guinea pigs (3, 4) and on volunteer human subjects (5).

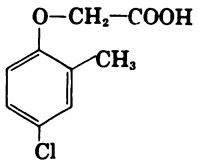
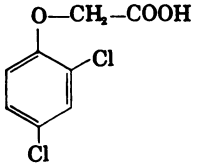
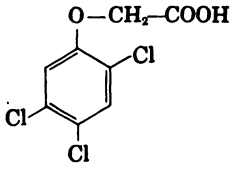
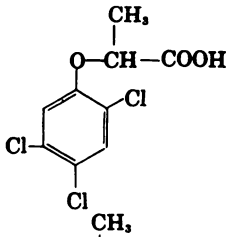
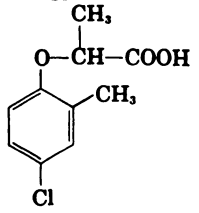
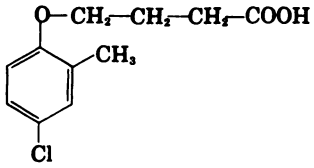
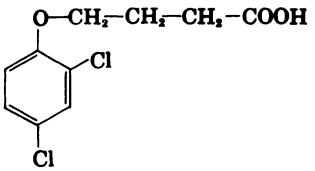
III. ORGANIC HERBICIDES

A. Chlorinated phenoxy-acids

Chlorinated compounds of phenoxy-acetic acid, propionic acid, and butyric acid, have been very extensively used within the past 15 years as herbicides under the common name of "hormone weedkillers." They stimulate parts of susceptible plants, particularly within the group of dicotyledons, to excessive, uncontrolled growth, which causes the plants to die (109). The most important compounds, which in the forms of water-soluble salts or lipoid-soluble esters constitute the active components of commercial preparations, are listed in Table 1, where the LD50 values in rats are also given. In addition to the compounds listed in the table, *p*-chlorophenoxyacetic acid (4-CPA), sodium 2-(2,4-dichlorophenoxy)ethyl sulphate (2,4-DES-sodium, Sesone, SES), and γ-(2,4,5-trichlorophenoxy)butyric acid (2,4,5-TB, 4-(2,4,5-TB)) are used as herbicides of this type.

TABLE 1

Chlorinated phenoxy-acids

Compound	Formula	Common or Abbreviated Names	LD50, mg/kg by Peroral Administration to Rats	Ref. No.
4-Chloro-2-methyl-phenoxy-acetic acid		*MCPA*,*†‡ MCP, 4K-2M	700	(89)
2,4-Dichloro-phenoxy-acetic acid		*2,4-D**†‡	375	(89)
2,4,5-Trichloro-phenoxyacetic acid		*2,4,5-T**†‡	500	(89)
α-(2,4,5-Trichloro-phenoxy)propionic acid		*2,4,5-TP*,† Silvex‡	650	(89)
α-(4-Chloro-2-methyl-phenoxy)propionic acid		*Mecoprop*,*† 2-(MCPP),‡ CMPP, MCPP	700–1500	(32)
γ-(4-Chloro-2-methyl-phenoxy)butyric acid		*MCPB*,*† 4-(MCPB)‡	700–1500	(32)
γ-(2,4-Dichloro-phenoxy)butyric acid		*2,4-DB*,*† 4-(2,4-DB)‡	700–1500	(32)

The acute toxicity following oral administration to a number of experimental animals is moderate. The LD50 as a rule is of the order of 300 to 700 mg per kilogram for the species examined (89), excepting dogs, which seem to be more susceptible, where the LD50 for both (2,4-dichlorophenoxy)acetic acid (2,4-D) and 2,4,5-T has been found to be 100 mg/kg (27). Experiments with oral administration of various salts and esters of 2,4-D as pure chemicals and as commercial preparations showed no significant difference in toxicity to a number of small animals from that of the free 2,4-D acid (53, 89).

Short-term studies on rats revealed no signs of reduced intake of food or inhibition of growth in response to admixture of 2,4-D at 400 p.p.m. in the fodder for 30 days or 1000 p.p.m. for 14 days. Subcutaneous injection of 50 to 100 mg 2,4-D per kg to mice daily for 90 days had no demonstrable effect on the general condition, fertility, or tissue histology (53). In Table 2 are recorded the results of feeding phenoxy-compounds to larger animals. Except for the rather considerable toxic effect on sheep of 2,4,5-TP, administered in the form of propylene glycol butyl ether esters, these experiments showed that the large herbivores seem to tolerate prolonged ingestion of phenoxy-compounds to the same extent as rats. In dogs, on the other hand, these compounds were found to have a pronounced toxic action: 20 mg/kg given for 2 to 3 weeks produced severe, fatal poisoning.

Parenteral and oral administration of toxic doses of 2,4-D to experimental animals brings about a characteristic complex of signs and symptoms (18, 27, 53), which has been studied particularly in dogs. After a few hours the animals display a disinclination to move. This passiveness is gradually aggravated, and a picture of myotonia develops with rigidity of the skeletal muscles and ataxia. The condition may improve transitorily with movement. In severe cases the animals show progressive apathy, depression, and muscular weakness, especially of the hindlegs, with periodic, clonic spasms, and, finally, coma. The muscular signs are accompanied by marked anorexia; frequently, irritation of the nose and eyes is indicated by scratching reactions. Further, bleeding from the nose and mouth may occur, as well as diarrhea with blood-stained stools. Local irritation of the alimentary tract often causes vomiting. However, this sign may be absent, even after oral administration to dogs (27). Autopsy may reveal necrotic ulcers of the oral mucosa and signs of irritation with histologically demonstrable inflammatory changes and necrosis of the small intestinal mucosa, as well as focal necrosis in the liver (27, 53) and degeneration of the renal tubules.

When given by mouth to dogs, even in fatal cases 2,4,5-T has produced only weak signs in the forms of ataxia and stiff movements of the hindlegs (27).

As for the human response, a report is available (9, 75) of a man who in a self-experiment consumed 500 mg of 2,4-D daily for 3 weeks, with no perceptible effect. A case of acute fatal poisoning has been reported from Denmark, where a young farm worker committed suicide by oral ingestion of not less than 6500 mg of 2,4-D. When found, the body showed signs of having been subject to violent convulsions before the occurrence of death. The changes post mortem were unspecific hyperemia of the lungs, liver, and brain (78).

TABLE 2

Chlorinated phenoxy-acids; short-term studies in dog, sheep, and cow

Compound	Animal Species	Daily Dose, mg/kg Body Weight	Result	Ref. No.
MCPA	Cow	30	Tolerated without detectable symptoms during 21 days	(24)
2,4-D	Sheep	100	Tolerated without detectable symptoms during 35 days	(85)
—	Dog	2–10	Tolerated without detectable symptoms during 90 days	(27)
—	Dog	20	3 of 4 animals died, 18th to 49th day	(27)
2,4,5-T	Sheep	100	Tolerated without detectable symptoms during 35 days	(85)
—	Dog	2–10	Tolerated without detectable symptoms during 90 days	(27)
—	Dog	20	4 of 4 animals died 11th to 75th day	(27)
2,4,5-TP	Sheep	100	Lethal after 11 doses	(85)

The action of ingested phenoxy-acid herbicides on muscular function, which is reminiscent of that following administration of halogenated acetic acid compounds (22, 23), suggests an interference with carbohydrate metabolism. Two cases of a transitory diabetiform condition observed in spraying personnel following work with chlorinated phenoxy-acid herbicides point in the same direction. However, hyperglycemia and glycosuria could not be reproduced with certainty in rabbits; only one out of five animals responded in this way in exploratory experiments, where the doses ranged from 125 to 500 mg/kg and the period of administration from 6 to 50 days (68).

The results of a long series of investigations into the toxicity to domestic animals and game of herbicidal preparations and treated crops suggested that acute poisoning caused by consumption of crops from sprayed fields is unlikely to occur (16, 24, 46, 75, 87), excepting that "grass-eating" dogs may be poisoned by newly sprayed lawns. Human beings and domestic animals are presumably liable to poisoning only by oral ingestion of highly concentrated preparations or spray solutions.

A special problem in connection with the use of chlorinated phenoxy-acid compounds is the tendency of the preparations—even in extremely low concentrations—to impart to water, milk, and other nutrients a very persistent chlorophenol-like odor and taste. Spilling of highly concentrated preparations close to wells or water courses has in several instances, by percolation through the strata, given a disagreeable taste to the water for long periods afterwards. Administration of 2,4-D to dairy cattle does not seem to result in excretion of biologically demonstrable amounts in the milk (75).

Very few toxicological data are available regarding other chlorinated *aromatic* acids, introduced alone or in combination as pre-emergence and selective herbicides for agricultural crops. 2,3,6-Trichlorophenyl-acetic acid (fenac‡), 2,3,6-trichlorobenzoic acid (2,3,6-TBA†‡, TBA, TCB) and 3-amino-2,5-dichlorobenzoic acid (*amiben*‡) are used for these purposes. The LD50 of 2,3,6-TBA after a single oral dose to rats was stated to be within the range of 700 to 1500 mg/kg (32).

B. Chlorinated aliphatic acids and their sodium salts

The chlorinated *aliphatic* acids possess more general phytotoxic properties. Some of these are used, therefore, for defoliation and desiccation of cultivated plants prior to mechanical harvesting. The most important compounds are: sodium trichloro-acetate (TCA-†‡ sodium), sodium monochloro-acetate (SMCA), and sodium-dichloropropionate (Dalapon-sodium*†‡), as well as the combined compound, 2-(2,4,5-trichlorophenoxy)-ethyl-,2′,2′-dichloropropionate (Erbon†‡).

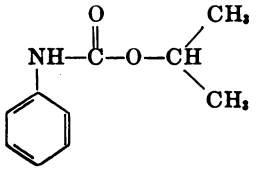
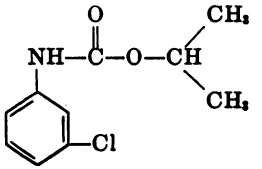
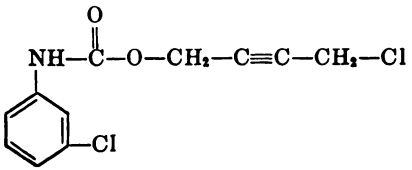
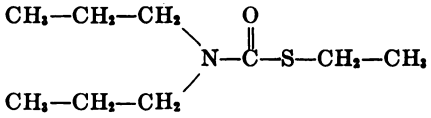
Studies on the acute toxicity of *sodium trichloro-acetate* have shown that this substance is not very toxic (118), the LD50 after oral administration being 3320 mg/kg for rats and 4970 mg/kg for mice. The animals quickly go into an anesthesia-like state, which lasts for 36 hours, to be succeeded by coma and death, or by awakening and survival. Sodium trichloro-acetate has a far less local-irritating action than the free acid, which can corrode the skin and mucous membranes.

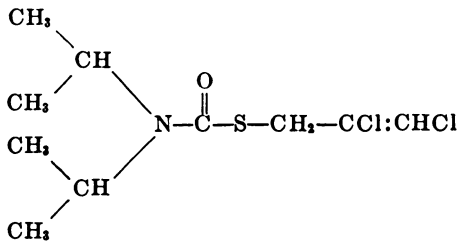
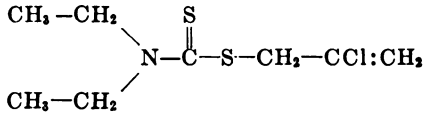
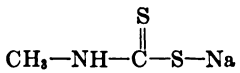
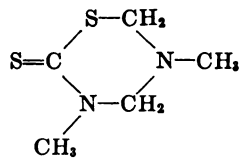
Sodium monochloro-acetate (SMCA) is considerably more toxic. Its action on bacteria and in the animal organism is reminiscent of that of other monohalogen-substituted acetic acid compounds, such as monoiodo- and monobromacetic acid, the enzyme-inhibiting and bacteriostatic properties of which have been thoroughly studied (*vide* 22). The LD50 after oral administration has been found to be 76 mg/kg for rats, and 80 mg/kg for guinea pigs (118), and of the same order for geese (20), whereas for mice the toxicity is somewhat lower, the LD50 being 255 mg/kg (118). In the small experimental animals apathy and loss of weight were noticed, and in the fatal cases death occurred within 3 days. The fatal oral dose for young cattle was found to lie within the range of 100 to 150 mg/kg. Colicky-like restlessness and incoordination were observed, developing in the course of 4 to 5 hours into universal fascicular twitchings, gnashing of the teeth, anxiety, dyspnea, and tachycardia. Coma and death followed after 9 hours (23). This picture, which is probably referable to blocking of oxidative metabolic processes, is reminiscent of that seen in pigs (22) and dogs (6) poisoned with monobromacetic acid. The gross and microscopic findings at autopsy were likewise identical with those described for monobromacetic acid-poisoned pigs (22).

Sodium 2,2-dichloropropionate (*Dalapon*) has become of particular interest owing to its herbicidal action on monocotyledons, such as grasses, in relatively small quantities, therefore being useful as a selective herbicide in certain crops of cultivated plants. Dalapon is absorbed by plants and then translocated. On this

TABLE 3

Carbamates

Compound	Formula	Common or Abbreviated Names	LD50, mg/kg by Peroral Administration to Rats	Ref. No.
Iso*propylcarbanilate*, isopropyl-N-phenyl-carbamate		Propham,*† IPC‡	1000	(119)
Iso*propyl*-m-*chloro-carbanilate*, *iso*propyl-N-(3-chloro-phenyl) carbamate		Chloropropham,*† CIPC,‡ chloro-IPC	5000	(115)
4-Chlorobut-2-ynyl-m-*chlorocarbanilate*, 4-chloro-2-butynyl-N-(3-chlorophenyl) carbamate		Barban(e),‡ Carbyne®	600	(36)
Ethyl-NN-dipropylthiolcarbamate		EPTC,‡ Eptam®	3160	(100)

2,3-Dichloroallyl-di-isopropyl thiolcarbamate		Avadex®	395	(119)
2-Chloroallyl-NN-diethyl-dithiocarbamate		*CDEC*,†‡ Vegadex®	850	(119)
Sodium N-methyl dithio-carbamate dihydrate		SMDC,‡ metham-sodium, Vapam®	820	(29)
3,5-Dimethyltetrahydro-1,3,5,2H-thiadiazine-2-thione		DMTT,‡ Mylone®	500	(119)

account, prolonged feeding experiments have been conducted with a view to assessing the possible risk involved by ingestion of residues in vegetables. The toxicity of the substance has been studied from several aspects through a comprehensive series of experiments (81). Administration of single doses to a number of small experimental animals has given LD50 values for rats, mice, guinea pigs, rabbits, and chickens within the range of 4000 to 9000 mg/kg. Two young cattle survived 1000 mg/kg given by mouth daily for 10 days. Beyond transitory symptoms in one of these (anorexia, diarrhea, indisposition), no signs of a toxic action were found by clinical or pathological examination. After oral administration of 15, 50, and 100 mg/kg daily to dogs for one year, blood and urine analyses, as well as liver function tests and histological examination of tissues revealed no signs of a toxic action, beyond an increased weight of the kidneys following the dose of 100 mg/kg. Examination of tissue specimens from the dogs showed up to 78 p.p.m. of Dalapon in kidney and liver tissues (81).

Feeding of rats with Dalapon for 2 years in doses of 100, 300, and 1000 p.p.m. in the fodder, corresponding to about 5, 15, and 50 mg/kg daily, was tolerated with no signs of a toxic action, apart from a minor increase in kidney weight on the largest dose. In these experiments with 1000 p.p.m., 10 to 30 p.p.m. of Dalapon was found on chemical analysis of the liver and kidney, and 20 p.p.m. in milk. Thus, cumulation does not take place. In rats, reproduction and lactation proved to be uninfluenced through three generations with daily administration of 300 to 3000 p.p.m. of Dalapon in the fodder (81).

The local-irritating action of Dalapon has been studied on rabbits, the skin of which was exposed daily for 10 days to a 10% aqueous solution. No more than signs of a mild, transitory irritation was seen (81).

C. Carbamates and allyl alcohol

Within this group of herbicides, which, as shown in Table 3, comprises carbamates, thiocarbamates, and dithiocarbamates, is a number of compounds which are used especially as pre-emergence or selective herbicides on certain crops. Propham and chlorpropham have also been used to prevent potatoes intended for consumption from sprouting while stored. The toxicity of these compounds with prolonged ingestion is therefore of particular interest.

Propham (O-*Iso*propyl N-phenyl carbamate, IPC). Various investigations have shown that carbamate esters possess a carcinogenic action. Thus intraperitoneal injection of *iso*propyl carbamate raised the frequency of lung tumors in a strain of mice from 17 to 90% (66). The idea of inquiring into a possible carcinogenic action of Propham, which splits off aniline by acid hydrolysis, therefore suggested itself. However, with prolonged oral, intramuscular, and intrapleural administration of Propham to rats and mice, no signs of a carcinogenic action were found (56). This is in agreement with the results of experiments on groups of four rats each, given 400, 800, and 1600 p.p.m., respectively, daily in the fodder for 3 months. No signs were demonstrable here of a toxic action on the general condition, growth, or fertility, and no pathological changes were seen at autopsy or on histological examination of the tissues (101).

Experiments with the chemically closely related *Chlorpropham* (*iso*propyl-N-[3-chlorophenyl] carbamate, CIPC) have shown it to have a very low acute toxicity to rats and rabbits, LD50 by oral administration having been found to be of the order of 5000 mg per kg for both species (115). In feeding experiments on male rats given 310 to 20,000 p.p.m. for 90 days, no effect was observed on growth. Doses of 1250 p.p.m. and higher produced an increase in weight of their livers, without histological changes being demonstrable (116).

In the light of the above investigations, the observation of the development of skin tumors following painting of the back skin of Propham- and Chlorpropham-fed rats with croton oil is of considerable theoretical interest (34). However, comprehensive feeding experiments (67) with administration of 2000 p.p.m. through 2 years to rats and 1 year to dogs revealed no carcinogenic effect. Feeding at 20,000 p.p.m. provoked in both species signs of a toxic action, which was manifested in rats by retarded growth, increased mortality of the male animals, and increased liver and kidney weights, though without demonstrable histological changes. In dogs, retarded growth, increased weights of liver, kidney, and spleen, and splenic congestion were noted (67).

Barbane (4-chloro-2-butynyl-N-[3-chlorophenyl]carbamate) displays a somewhat greater acute toxicity than the Propham compounds, the LD50 after oral administration having been found to be 600 mg per kg for the rat and rabbit, and 240 mg/kg for the guinea pig. Dermal application of 1600 mg/kg over a period of 24 hours caused no deaths among rats. Oral administration of 9, 19.5, and 37 mg/kg daily for 22 days produced no toxic reaction, whereas 75 mg/kg over the same period effected loss of weight. Feeding experiments with rats showed no toxic action of 150 p.p.m. for 18 months (36). Barbane is a potent skin-sensitizing agent in man, in whom allergic reaction with rash develops at subsequent contact. Protection against cutaneous contact is therefore necessary during its use. Plastic (polyvinyl chloride) seems to be a more suitable protective material than rubber (36).

SMDC (sodium N-methyl dithiocarbamate dihydrate, metham-sodium) has a special sphere of application, being used for killing weed seeds, soil nematodes, and the like by so-called soil sterilization. When applied in the soil it liberates gaseous *methylisothiocyanate*, the active substance, which is also available commercially as an aqueous solution (Trapex) for similar purposes. The LD50 of SMDC by oral administration to rats has been stated to be 820 mg/kg (29). The toxicity of *methylisothiocyanate* is considerably higher, the LD50 being 97 mg/kg (82). The main toxicological interest attaches, however, to the pronounced locally irritating action of these substances on the skin and mucous membranes, especially those of the respiratory organs, as well as the possibility of absorption of toxic amounts by these routes. The LD50 of SMDC after dermal application to rabbits has been found to be 800 mg/kg (29), whereas daily rubbing of methylisothiocyanate in 10% ethanol for 9 weeks into rabbit ears gave no more than a weak reaction (82).

Allyl alcohol. This unsaturated alcohol has the same range of application as SMDC and methylisothiocyanate; it is applied in solution to the soil, where its

action is strong, but of short duration, so that cultivated plants can be sown about two weeks later and grow without the interference of weed seedlings. Allyl alcohol has a strong locally irritating action and can be absorbed through the alimentary tract, the lungs, and intact skin. Extensive investigations of its toxicity have been made on experimental animals. The early literature, to which Miessner (74) contributed significantly by his investigations from 1891, has been summarized thoroughly (79). The toxicity and mechanism of poisoning have been studied in the United States within recent years (30, 65, 94, 95). LD50 values after oral administration to the mouse, rat, and rabbit ranged from 50 to 100 mg/kg, and after percutaneous administration to rabbits, from 45 to 90 mg/kg. Some time after the administration the animals were found apathetic, but not anesthetized, as they reacted strongly to pain stimuli. Lacrimation was seen, and often also increased secretion by salivary and gastroenteric glands, increased motility of the intestines, dyspnea due to pulmonary effusion, loss of weight, hemoconcentration, and vasodilatation. Autopsy revealed congestion of the organs as well as periportal necrosis (30, 65). Local application to rabbit skin produced only transitory signs of irritation. Instillation into the eyes of rabbits resulted after 1 hour in redness and swelling, which were intensified in the course of 24 hours. In some instances keratitis was seen, but the condition returned to normal within a week (30).

In acute inhalation experiments on rats, half of the exposed animals died in the course of 1 hour at an air concentration of 1060 p.p.m.; 165 p.p.m. for 4 hours or 76 p.p.m. for 8 hours gave the same result. Experimental volunteers exposed to air concentrations of 0.78 to 25 p.p.m. for 5 minutes one to three times weekly over a period of 50 days, developed no signs of pulmonary discomfort or affection of the CNS. The subjects could barely detect 0.78 p.p.m., while irritation of the nasal mucosa was first noticed at 6.25 to 12.5 p.p.m., and eye irritation at 25 p.p.m. (30).

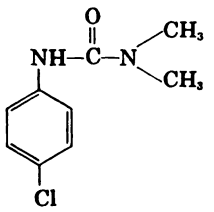
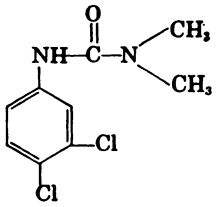
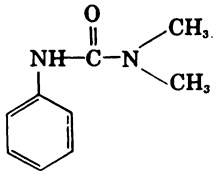
Acrolein (acrylic aldehyde), the aldehyde corresponding to allyl alcohol, has been used for control of water plants and algae by introduction under water. The substance has the disadvantage of being highly toxic to fish, but this seems to be compensated for by its quick elimination. The LD50 after single subcutaneous administration is 30 mg/kg for mice and 50 mg/kg for rats. Moderate anesthesia occurs, as well as a few convulsive fits and dyspnea, especially in mice. Autopsy with histological examination of tissues has revealed pulmonary edema, chiefly perivascularly and hyperemia, slight fatty degeneration of the liver, and focal inflammatory processes in the kidney. At poisoning after inhalation, where 0.3 p.p.m. for 30 minutes has a lethal effect, the histological changes—edema, hyperemia, and epithelial cell degeneration—are confined to the lungs (95).

D. Substituted ureas

The most important compounds belonging to this group of herbicides have been listed in Table 4, in which it is shown also that these compounds have a low acute toxicity when administered by mouth to rats. For 3-(*p*-chlorophenyl)-1,1-

TABLE 4

Substituted ureas

Compound	Formula	Common or Abbreviated Names	LD50, mg/kg by Peroral Administration to Rats	Ref. No.
N-(p-*Chlorophenyl*)-*N*^{1}*N*^{1}-*dimethylurea*		Monuron,*†‡ CMU	3500	(28)
N-(*3,4-Dichlorophenyl*)-*N*^{1}*N*^{1}-*dimethylurea*		Diuron,†‡ 3,4-DDU, DMU	3400	(28)
NN-Dimethyl-N^1*-phenylurea*		Fenuron,†‡ PDU	7500	(91)

dimethylurea (Monuron) the approximate lethal dose by single oral administration to guinea pigs and rats has been set at 670 and 1500 mg/kg, respectively (28). To the same group belong also N-butyl-N^1(3,4-dichlorophenyl)-N-methylurea (Neburon†‡), 1,3-di(2,2,2-trichloro-1-hydroxyethyl)urea (Dichloral urea, DCU‡, DU), and N-cyclooctyl-N^{1}N^1-dimethylurea (OMU).

The substituted urea derivatives destroy numerous species of plants, and their activity persists for a long time. They are used in large doses for eradication of all vegetation of farmyards, railway tracks, roadsides, *etc.* They may also be used in much lower concentrations on cultivated crops, such as asparagus. Owing to the long persistence of these substances, residues may be present in harvested crops. In feeding experiments on rats given Monuron at 25, 250, and 2500 p.p.m. for 2 years, no effect was observed on survival or frequency of tumors, as compared with control groups and in the colony of normal rats. The conclusion was drawn that "there was no indication that Monuron is cancerogenic" (54). In the group given 2500 p.p.m. the male rats were seen to lose weight after only one month of feeding. During the experiment mild anemia was also found, and at the end the

weights of the liver and spleen had increased. On histological examination of tissue specimens none of the groups presented changes attributable to an action of Monuron. In experiments on dogs, which received in their diet 2.5, 12.5, and 25 mg Monuron per kg for one year, no signs of toxicity were seen during the experiment, and at autopsy with histological examination of tissue specimens no changes were noticed that seemed to originate from feeding with Monuron (54).

Rats given 500 p.p.m. of *Fenuron* in the diet for 90 days tolerated this dose with no signs of poisoning (91). *Diuron* was likewise tolerated at 50 p.p.m. While 5000 p.p.m. of this compound for 90 days caused no deaths, but loss of weight, a fall in the number of red blood corpuscles, and pathological changes in the spleen were noted (28).

Preliminary experiments using Monuron and Diuron on guinea pigs have shown no signs of allergic skin sensitization. Neither have such reactions been observed in experimental subjects or factory employees working with these compounds (28).

E. Triazines

The announcement of the phytotoxic and plant-growth-regulating properties of a series of aminotriazines (41), especially the 2-chloro-2,4-bis(ethylamino)-1,3,5-triazine compound, Simazine, initiated the synthesis of a great number of herbicidal derivatives. The two most commonly employed of these are shown in Table 5, whereas the compounds known under the names of: Propazine‡(2-chloro-

TABLE 5
Triazines

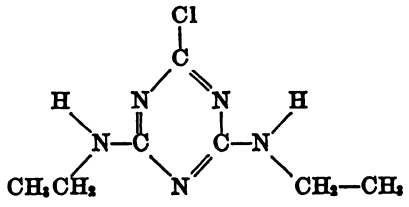
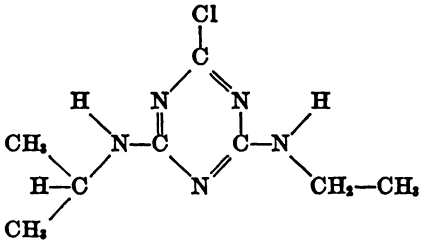
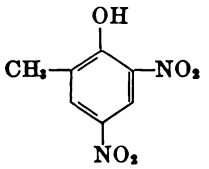
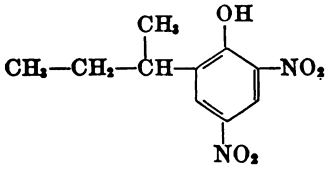
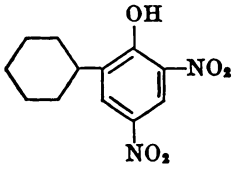
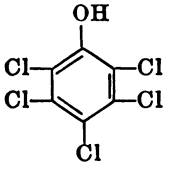
Compound	Formula	Common Names	LD50, mg/kg by Peroral Administration to Rats	Ref. No.
2-Chloro-4,6-bis (ethylamino)-1,3,5-triazine		*Simazine*†‡	5000	(42)
2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine		*Atrazine*‡	1750	(43)

TABLE 6

Substituted phenols

Compound	Formula	Common or Abbreviated Names	LD50, mg/kg by Peroral Administration to Rats	Ref. No.
2-Methyl-4,6-dinitrophenol		*DNOC*,*† DNC,‡ dinitrocresol	40	(32)
2-s-Butyl-4,6-dinitrophenol		*Dinoseb*,*† DNBP,‡ DNOSBP	50	(32)
2-Cyclo-hexyl-*4,6-dinitrophenol*		*Dinex*, DNOCHP		
Pentachlorophenol		PCP†‡	80–200	(32)

4,6-*bis*[*iso*propylamino]-1,3,5-triazine), Trietazine‡ (2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine), Ipazine‡ (Isodiazine, 2-chloro-4-diethylamino-6-*iso*propylamino-1,3,5-triazine), Simetone‡ (2,4-*bis*[ethylamino]-6-methoxy-1,3,5 - triazine), Prometone‡ (2,4 - *bis*[*iso*propylamino] - 6 - methoxy - 1,3,5-triazine), and Atratone‡ (2-ethylamino-4-*iso*propylamino-6-methoxy-1,3,5-triazine), are still being used mainly experimentally.

These compounds are almost insoluble and persist for a long time in the soil. They have been used mainly for eradication of all vegetation as well as for local weedkilling under fruit trees and shrubs. Certain species of plants, *e.g.*, asparagus and maize or corn, are, however, resistant to the herbicidal action of the triazines. Their use on areas with these cultivated plants is therefore practicable but involves a risk of residues in crops for consumption.

Studies on the toxicity of *Simazine* (42) showed that the LD50 after oral administration to mice, rats, rabbits, chickens, and pigeons in all cases exceeded 5000 mg/kg, whereas all rats survived daily doses of 2500 mg pure Simazine per kg for 4 weeks, and 1250 mg of a commercial preparation per kg. Rats fed for two years on a diet containing 1, 10, and 100 p.p.m. of Simazine revealed no signs of

toxicity (46a), and screening tests for various acute actions, such as spasmolysis on the isolated intestine and analgesia in mice, did not demonstrate significant activity (46a).

The LD50 of *Atrazine* (2-chloro-4-ethylamino-6-*iso*propylamino-1,3,5-triazine) (43) after a single oral administration was found to be 1750 mg/kg for mice and 3080 mg/kg for rats, while a daily dose of 400 mg/kg through 6 weeks proved fatal to half of the test rats.

F. Substituted phenols

Dinitrophenols. The checkered history of the dinitrophenols also includes a chapter on their applicability as herbicides. In agriculture these compounds are used also as insecticides, acaricides, and ovicides, for potato haulm destruction, pre-harvest desiccation of leguminous seed crops and apple-thinning sprays. The chances of contact are therefore great, and their users are often poisoned when protective measures are disregarded.

Three derivatives are commonly used: DNOC (DNC, 2-methyl-4,6-dinitrophenol), Dinoseb (DNPB, 2-sec.butyl-4,6-dinitrophenol), and Dinex (DNOCHP, 2-cyclohexyl-4,6-dinitrophenol). The chemical configurations and LD50's for rats after oral administration are shown in Table 6. The mechanism of toxic action which is based on the uncoupling of oxidative phosphorylation, has been studied in detail; a survey has been given in this journal (17). A great number of toxicological data have been given in Handbook of Toxicology (77), and poisoning of man and domestic animals has been reported in recent surveys (12, 32, 40, 72, 86, 88). Clinical accounts are available from Belgium (52) and Great Britain (15), among others. Up to 1950 seven British cases had been reported of fatal poisoning with DNOC used as a weedkiller. Countermeasures against poisoning (14) have since been satisfactory in Britain, no fatal accidents having occurred after their introduction (12, 32).

Pentachlorphenol. Like the dinitrophenols, pentachlorphenol is an effective uncoupler of oxidative phosphorylation. The mechanism of toxic action has been studied in experiments with molluscan and mammalian tissues as well as on enzymes (110, 111, 112, 113). It seems to be due to inhibition of the intracellular transfer of energy-rich phosphates as well as their synthesis. In agreement with this, the symptoms of intoxication include acceleration of respiration, hyperpyrexia, hyperglycemia, glycosuria, and promptly occurring motor weakness. As in cases of dinitrophenol poisoning, *rigor mortis* sets in early and is very pronounced (26, 45, 64, 71).

The acute toxicity of pentachlorphenol as well as that of its sodium salt have been studied by oral, subcutaneous, and dermal administration of single doses to rats and rabbits (26, 64, 71, 102), and by single subcutaneous injections into dogs (71). The LD50's and the minimum lethal doses were found to vary considerably, ranging from 27 to 550 mg/kg. The highest toxicity was noted for pentachlorphenol dissolved in mineral oil (fuel oil) given by mouth to rats, and the lowest for the sodium salt administered in the same way to rabbits. After dermal application, mineral oil solutions are likewise more toxic than solutions in vegetable

oil and in water (64). Furthermore, the local reaction, which may manifest itself by changes from erythema to grave dermatitis, is stronger with mineral oil as vehicle (64, 71).

The results of short-term studies on a number of animal species suggest a certain degree of cumulative action, especially after subcutaneous injection (71); signs of such have also been seen after oral administration to rats and cats (26). In experiments on calves, on the other hand, cumulative action has not been observed (51).

From the practical use of pentachlorphenol, this compound is well known as a skin irritant (12); in addition, toxic amounts may be absorbed through the skin. In relation to its use as a timber-preservative, human cases of poisoning have occurred, some of which have been fatal (73, 107).

Sodium pentachlorphenate in aqueous solution with mineral oil added, used as a herbicide in pineapple plantations in Australia, has been described as the cause of poisoning of nine workers, five of whom died. In one, who died after 21 hours, pentachlorphenol was demonstrated by chemical analysis of tissue specimens in quantities of 2 to 14.5 mg per 100 g tissue (45).

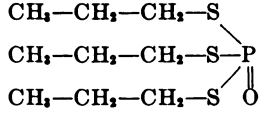
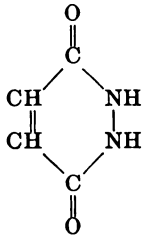
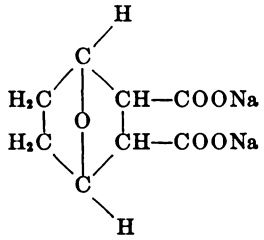
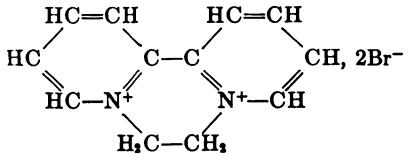
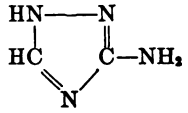
In cattle, cases of poisoning have been described which ran a fatal course within 24 hours of oral ingestion of 5% pentachlorphenol in kerosene (97). Mild signs and symptoms of poisoning in sheep and cattle have followed 25 mg/kg (85).

G. Miscellaneous organic herbicides

1. Tributyl phosphorotrithioate (DEF). Organophosphates have become very extensively used as insecticides within agriculture and horticulture. A comprehensive literature is available on the toxicity of these compounds, related to their cholinesterase-inhibiting action (55). In studying DEF, which is used as a defoliant in cotton fields, attention has been focused on the relationship between the toxicity and the inhibiting action on the cholinesterase activity in different organ tissues (76). The LD50 after oral administration to rats is 325 mg/kg (Table 7). With daily intraperitoneal injections of 50 mg/kg into rats for up to 60 days no signs of poisoning were observed, although after sacrifice cholinesterase of brain tissue was found to be 14% of the average in control groups. Injection of 100 mg/kg was lethal after 5 to 30 days. In acute poisoning experiments depression and inactivity were seen after one hour. These symptoms persisted for 24 to 48 hours, unless irritability or manifestation of pain or tremor was produced by external stimuli. The depression developed in some cases into muscular weakness with rigidity. Not till 2 to 6 hours after injection did the animals also display the usual signs of anticholinesterase poisoning: profuse urination, salivation, and lacrimation, and respiratory impairment increasing to respiratory paralysis and death (76). The cholinesterase activity of the red blood cells and brain was often poorly related to the cholinergic signs, often with freedom from any signs or symptoms despite a low activity level (76). Having been observed also in cases of poisoning with other organic phosphorus compounds (39, 63), this fact does not militate against the hypothesis of cholinesterase inhibition as an etiological factor in the mechanism of poisoning. The somewhat differing manifestations of poisoning, and the failure of prophylactic and therapeutic effects of enormous

TABLE 7

Miscellaneous organic herbicides

Compound	Formula	Common or Abbreviated Names	LD50, mg/kg by Peroral Administration to Rats	Ref. No.
S,S,S-tributyl phosphorotrithioate		*DEF*	325	(76)
1,2,3,6-tetrahydro-3,6-dioxopyridazine		*Maleic hydrazide*, MH‡	4000	(13)
Disodium 7-oxabicyclo-(2,2,1)heptane-2,3-dicarboxylate, Disodium 3,6-endoxohexahydrophthalate		*Endothal-sodium*†‡	80	(32)
9,10-dihydro-8a,10a-diazoniaphenanthrene dibromide, 1,1¹-ethylene-2,2¹-dipyridylium dibromide		*Diquat*,*†‡ Reglone®	400–440	(83)
3-amino-1,2,4-triazole		Amitrole,‡ ATA, amizol, amitol	25000	(90)

doses of atropine (76) suggest, however, that other factors also contribute towards the toxic action of DEF.

2. Maleic hydrazide (1,2,3,6-tetrahydro-3,6-dioxopyridazine) is used for spraying on roadsides, hedges, and the like, to facilitate and reduce the work with cutting, *etc.* The growth-inhibiting properties are utilized further by spraying the compound on root crops 2 to 4 weeks before harvesting, as this greatly reduces the tendency to sprouting during storage.

In experiments on a number of small animals, the acute and chronic toxicities of this compound were found to be low. Thus, for instance, the LD50 after oral administration to rats was 4000 mg/kg, while prolonged feeding experiments on rats with 10,000 p.p.m. of maleic hydrazide in the fodder showed no signs of a toxic action within the normal life span (13). The demonstration of the fact that in *Vicii faba* roots maleic hydrazide not only inhibited the growth of cells, but also caused breakage of the heterochromatin in the chromosomes (25) aroused a great interest in ascertaining whether animal cells might also be susceptible to this action, or whether it is specifically directed against plant cells. This is important, because the ability of substances to produce chromosome breakage may be accompanied by carcinogenesis. In thorough investigations, comprising weekly subcutaneous injections into mice and rats of 500 mg/kg for 100 weeks, as well as feeding experiments over the same period with 10,000 p.p.m. of maleic hydrazide in the diet, no signs of a carcinogenic action were demonstrable. Tests for a possible co-carcinogenic action on application together with croton oil to mouse skin revealed no greater tumorigenic action than that of the oil alone. Implantation of maleic hydrazide pellets in the bladder of mice did not give rise to tumor formation, and administration of 125 mg of the compound per kg to tumour-affected rats had no effect on the tumour growth or cell mitoses. In experiments with tissue cultures of mouse epidermis and guinea-pig skin, no effect was seen on cell division, mitosis, or tissue respiration (13).

The fate of maleic hydrazide has been studied in rabbits. After oral administration of 100 mg/kg, the rabbits excreted 43 to 62% unchanged in the urine in 48 hours. Coupling products were not detected, and the fate of the remaining 40% of the administered amount could not be determined (13).

3. Endothal-sodium (disodium 3,6-endoxohexahydrophthalate), which has strong plant-damaging properties, is used particularly as a defoliant and desiccant in leguminous crops, and has also been tried as a pre-emergence herbicide, *e.g.*, for sugar beets. The compound, which is closely related to cantharidin, is very toxic. After oral administration to rats, the LD50 has been found to be 80 mg/kg (32), whereas the lethal dose by intravenous injection into rabbits and dogs is of the order of 5 to 10 mg/kg (44). Shortly after administration, scratching of the nose was observed, and in the dogs, intermittent retching and vomiting also occurred for 2 hours, followed by death or recovery. In the rabbits, headshaking and irregular, greatly accelerated respiration were noticed (98). For both animal species, death was attributed to respiratory failure. In experiments with isolated ventricles of frog hearts and rabbit atria functional depression was seen in response to a 1 in 20,000 solution of Endothal-sodium (44). Hence, cardiac de-

pression has been supposed to be the cause of death. However, intravenous injection of Endothal into anesthetized dogs, atropinized as well as non-atropinized, caused a fall in blood pressure and respiratory failure, whereas changes of the ECG were first noticed in association with severe respiratory impairment in the terminal phase. While cats reacted in the same way as dogs, although with a less pronounced fall in blood pressure, domestic fowls were found to be insensitive to doses four times larger than those which were active on dogs and cats (98). The effects of Endothal both *in vitro* and *in vivo* were found to be characterized by manifesting themselves only after a long latency (98). This points towards a metabolite as the proper active factor.

Application of a 10 to 20% aqueous solution to the skin produced erosions which developed into necrosis, in some cases resulting in death owing to cutaneous absorption (44). The LD50 after dermal application to rats was 750 mg/kg (32).

4. Diquat (*Reglone*). Diquat (9,10-dihydro-8α,10α-diazoniaphenanthrene dibromide) has been proposed as an agent to produce desiccation and defoliation prior to harvesting, destruction of potato haulm, and as a pre-emergence and a total herbicide.

The LD50 after oral administration to rats was 400 to 440 mg/kg, whereas the LD50 after subcutaneous injection was 20 mg/kg, with death occurring in the course of 5 to 7 days. At autopsy, the intestinal canal, especially the cecum, was distended; histological examination revealed signs of gastrointestinal irritation, and in the lungs, thickened alveolar walls, particularly after large doses (83).

Intraperitoneal injection of 500 mg/kg to rats produced cyanosis and convulsions, culminating in death after 2 hours. Subcutaneous injection of 1 mg/kg into rats for 3 weeks caused no signs of toxicity. Similarly, feeding experiments to rats over 14 months with 500 p.p.m. in the diet disclosed no carcinogenic or toxic action (83). Following oral administration of C^{14}-labelled Diquat, 90 to 97% of the amount of activity given was recovered in the feces in the course of 48 hours (83). This, correlated with the difference in toxicity after oral and parenteral administration, suggests minimal absorption from the gastrointestinal canal.

5. Aminotriazole (3-amino-1,2,4-triazole) is herbicidally active against numerous species of plants. After absorption, it is translocated through the root as well as through the foliage. It breaks down rather quickly in the soil, and the exposed plants become chlorotic, as aminotriazole seems to interfere with chlorophyll production (47).

In animal experiments, aminotriazole showed a low acute toxicity, the LD50 after oral administration having been found to be 14,700 mg/kg for mice (114) and about 25,000 mg/kg for rats (90). No signs of poisoning were seen after intravenous injection of 1750 mg/kg to a cat (90), of 1600 mg/kg to mice (90), or 1200 mg/kg to a dog (114). A single intraperitoneal dose of 4000 mg/kg was tolerated by mice, whereas 21 doses of 1000 mg/kg each to rats, distributed over 45 days, produced an increase of the thyroid weight of 328% in males and 410% in females, while at the same time the growth and intake of food were found to be normal (90).

In feeding experiments on rats extending over 68 weeks, no effect was seen on the growth or intake of food at 10 and 50 p.p.m. in the diet, as compared with

controls, whereas 100 p.p.m. caused a decrease in growth and food intake in male rats during the last few experimental weeks. However, in male rats given 50 p.p.m. the thyroid became enlarged after 13 weeks (114). Investigations into the effect on the thyroids of rats of 2 years of feeding with aminotriazole are stated to have given the following results: In the control group, there was found one case of cystic follicle with papillary changes, while among the animals given 10 p.p.m. one out of ten examined presented adenoma; further, after 50 p.p.m. two out of 15 examined had adenoma and one apparently adenocarcinoma. Rats given 500 p.p.m. of aminotriazole in the diet for 17 weeks, which were then retained on a diet free of the compound for 2 weeks prior to sacrifice, appeared to have normal thyroids at the time of sacrifice (62).

The observation that rats fed with 100 p.p.m. of the compound for 2 years "developed a significant number of thyroid adenomas and adenocarcinomas," as well as the demonstration of residues of aminotriazole in marketed cranberries (31), caused prohibition of sale of cranberries and cranberry products of the 1958 and 1959 crops from certain parts of the United States. Furthermore, it resulted in an official announcement from the Secretary of Health, Education, and Welfare that the reason for the prohibition was "possible contamination by a chemical weedkiller, Aminotriazole, which causes cancer in the thyroid of rats" (37). In the ensuing discussion, doubts were raised as to whether the marked antithyroid action of aminotriazole can justly be characterized as carcinogenic (10, 62).

The mechanism of the antithyroid action of aminotriazole seems, on the basis of experiments on rats, to be identical with that of thiouracil derivatives (1a, 62). The absorption of I^{131} by the thyroid is depressed in both rats (1a) and humans (10), because its incorporation as organically bound iodine is obstructed (1a). Following injection of aminotriazole, a reversible inhibition has been noticed of the catalase activity in thyroid tissue (1a) as well as in kidney and liver tissues (49, 50, 104). However, to obtain a definite inhibition of the catalase activity, larger doses of aminotriazole are required than are necessary to depress the absorption of I^{131} by the thyroid (1a). Hence, inhibition of catalase activity can hardly account for the antithyroid action. Studies, *in vitro*, using purified catalase preparations from liver and red blood corpuscles, have under special experimental conditions shown irreversible inhibition (69). However, the results of experiments with thyroid tissue suggest that inhibition of thyroid peroxidase is the essential factor (2), a hypothesis that is borne out by the results of experiments with peroxidase from milk and vegetable tissue, which are likewise inhibited by aminotriazole (19). It should be added, however, that the question has not yet been clarified, since enzymes that are active in the purine metabolism of bacteria are also inhibited, in these cases reversibly by aminotriazole; this observation is utilized experimentally (84, 117).

IV. CONCLUSIONS

Apart from the fact that most information regarding the toxicology of the herbicides is as yet rather fragmentary—a situation which will be considerably improved when reports from the biological laboratories of industry become avail-

able to the public—it is important that attention not be confined to the toxicity of the original compounds. Their influence on plant metabolism might, for instance, block synthetic chains, leading to the accumulation of endogenous toxic products in vegetables. In this respect it has been shown that 2,4-D, applied in subtoxic amounts to such plants as sugar beets, increases the concentration of nitrate to twenty times the normal level. Consequently, feeding with the foliage involves a risk of poisoning (99). Attention has also been focused on the increase of cyanide in cyanogenic plants exposed to the action of herbicides (103).

As to the toxicity of metabolites of the herbicides themselves, which are formed in the soil and plants after their distribution, little is known. The problem has been touched in connection with investigations into the breakdown of herbicides by the aid of the micro-organisms in the soil. In particular, the decomposition of the chlorinated phenoxy-acids and the chlorinated aliphatic acids by soil bacteria and fungi has been submitted to extensive studies (*vide* 11, 57, 58, 59, 60, 93, 121). It appears that the breakdown of these compounds is almost complete, involving dehalogenation (57–60) and hydroxylation of the side-chain (93). Therefore, a persistent deleterious effect on the microflora of the soil need not be feared after use of the great majority of these organic herbicides (38). This is probably due to the fact that in most cultivated soils the populations of bacteria and fungi are so rich that there will always be found at least a few individuals that can adapt to almost any substance presented to them. These will synthesize new specific enzyme systems using the foreign substance as substrate. The resistant strains of micro-organisms will therefore multiply excessively, until the "substrate" has been decomposed (11). In general, the biotransformation of herbicides in soil does not seem to lead to the production of more potent compounds (11, 93, 121). Certain inorganic herbicides, *e.g.*, chlorate, may, however, have a deleterious influence on bacterial nitrification in the soil. By reduction of chlorate, hypochlorite may be produced, which has a very strong inhibitory action on the growth of the soil bacteria (1). Pentachlorphenol may have a harmful effect, especially on the soil fungi; various emulsifying and surface-active agents in the herbicidal preparations may also interfere with the soil flora (38).

The fates of the herbicides in plants have as yet been scarcely elucidated, but intensive studies are being carried on to clarify biotransformation in plants. The explanation of selective phytotoxicity has been founded on these studies. Decisive progress was gained when it was discovered that the herbicidally inactive 4-(2,4-dichlorophenoxy)butyric acid is converted by *beta*-oxidation to the active 2,4-dichlorophenoxyacetic acid in plants where specific *beta*-oxidase systems are present. These plants are harmed while species not possessing the specific enzymes are resistant (109). Conversely, the triazine derivative, Simazin, in nonsensitive plants is degradated by the presence of different factors such as catalase, peroxidase, and polyphenols to substances without phytotoxicity (46a). Great difficulties in analytical procedures have to be solved before the fates of herbicides in plants are clarified (92). However, there is reason to expect that a more rational basis will eventually be available, both for the study of the metabolism of herbicides in the animal organism, and for the planning of experimental in-

vestigations of the toxicity of the original compounds as well as of their metabolites. A knowledge of persistent metabolites in crops for consumption especially will be of very great importance in the study of long-term actions, including carcinogenic effects (35).

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