Overview of Potential Mutagenic Problems Posed by Some Pesticides and Their Trace Impurities

by Lawrence Fishbein*

This review principally addresses a number of aspects of usage of pesticides as well as populations at potential risk and attempts to highlight categories of pesticides whose structures or those of their metabolites and/or trace impurities, degradation and transformation products suggest an a priori mutagenic and/or carcinogenic risk.

The pesticides considered include: DDT, hexachlorobenzene (HCB), 2,4,5-T, pentachlorophenol, and various herbicidal precursors (e.g., carbamates, triazines) of nitrosamines and nitroso derivatives.

Structural features of a number of halo-unsaturated pesticides (e.g., dichloropropenes) were also reviewed from a viewpoint of contrasting their potential mutagenicity with that of vinyl chloride and vinylidene chloride. Additionally the mutagenicity of the organophosphorus pesticide Trichlorophon is contrasted with that of its degradation products.

Pesticidal agents constitute a prime area of human concern. Included in this category are insecticides, fungicides, herbicides, fumigants, acaricides, seed sterilants, soil nematocides, growth inhibitors, growth regulators, and chemosterilants.

A number of these agents are of major importance and are used in considerable amounts in such forms as granular formulations, dusts, powders, sprays, foams, and aerosols, and hence man can be exposed to these agents via handling of these agents per se, re-entry into a treated area, through ecological distribution, or via consumption of toxicant residues in food.

Apart from the dangers of acute and chronic poisoning, the possible mutagenic effects of such contaminations could threaten the genetic health of future generations, and hence it is of major importance that these effects be investigated. The major objectives of this report are to address the following questions: (a) What is the scope of usage of pesticides? (b) Are there categories of pesticides in which the compounds themselves, their metabolites, and/or degradation and transformation products as trace impurities have structures that suggest an a priori mutagenic and/or carcinogenic risk?

The pesticide industry uses approximately 1400 active ingredients formulated by 4600 companies at 7200 plants in the U. S. alone, to produce an estimated 35,000–50,000 separate products for an annual volume of 1.6 billion pounds (approximately 45% of world production) worth approximately 3 billion dollars as of 1975. Approximately 100 pesticide chemicals are responsible for the major use (e.g., as insecticides, herbicides and fungicides) (1).

Illustrative of the number of individuals who can be involved in the use of a specific pesticide is the example of the herbicide Treflan (Trifluralin; 2,6-dinitro - N,N - dipropyl - 4 - trifluoromethylaniline); 470,000 applicators and 38,000 field workers are believed involved in its use (1).

Although initially a relatively small number of people is exposed to high concentrations of pesticides, as are the spraying men in agriculture or the workers in the pesticide manufacture or formulation plants, most people are daily exposed to minute amounts of pesticide residues in their food, their households, etc. According to Seiler (2), the mutagenic potential of such substances may be relatively small, but the large population exposed to them could render the risk significant when weighed against the benefits of their use.

All organic pesticides, to a varying degree, are metabolized in living organisms and/or are degraded
environmentally (photolytically, chemically, thermally, microbiologically). The extent and nature of these transformations vary with the agent causing them, pesticidal chemical structure, physical form, and time being important parameters; the transformation of some of these agents occurs in a matter of minutes, while that of others requires months or even years. The chemical reactions involved include hydrolysis, oxidation, reduction, dehalogenation, desulfurization, nitrosation, ring opening, isomerization, and conjugation. These considerations are of fundamental importance in any meaningful mutagenic evaluation. Although it may be experimentally convenient to assess the purified chemical agent in question in diverse mutagenic tests systems, it is important to recognize the possibility of absorption or ingestion or a host of related and structurally unrelated entities, not only those arising from the metabolism and environmental degradation of the agent; but also including those precursors and degradation products attendant with the synthesis of the agent. This aspect arises because of both economic necessity and the possibilities that the reaction impurities possess sufficient pesticidal activity to warrant their inclusion in the product or that their physical and chemical properties preclude their facile removal. For example, DDT is made by condensation of chloral (trichloroacetaldehyde) and monochlorobenzene in sulfuric acid to produce a commercial product that illustrates almost to the extreme, the numbers of constituents that can be present in an important commercial pesticide. Besides containing the major product, p,p'-DDT (approximately 70%), technical DDT contains other isomers, degradation products, and reaction by-products: o,p'-DDT, p,p'-DDD, o,p'-DDD, bis(p-chlorophenyl)sulfone, chlorobenzene, p-dichlorobenzene, 2-trichloro-1-chlorophenyl ethanol, 2-trichloro-1-chlorophenylethyl-p-chlorobenzene sulfonate, o-chloro-α-β-chlorophenylacetamide and at least half a dozen other components. Of the reactants, chloral has been shown to be mutagenic (3, 4), and there may be a possible association between leukemia in man and carcinogenicity in experimental animals with exposure to dichlorobenzenes (5).

Hexachlorobenzene (HCB, perchlorobenzene) is an additional chlorinated benzene of toxicological and environmental concern. In the United States, approximately 90% of the estimated 8 million pounds of hexachlorobenzene is as a byproduct of perchloroethylene, trichloroethylene, and carbon tetrachloride manufacture. Most of the remaining production of hexachlorobenzene is as a by-product at more than 70 other manufacturing sites producing chlorine and certain pesticides. Approximately 45,000 lb is released into the environment during pesticide use. While HCB is used primarily as a fungicide to control bunt of wheat, it can also be formed as an impurity during the synthesis of the widely used herbicide DCPA (dimethyltetrachloroethylenephtalate, Dacthal) which can contain 10-14% HCB (6). The widely used fungicide pentachlorobenzene (PCNB, quintozone) can contain 1-6% HCB. HCB is also an intermediate in the production of pentachlorophenol (PCP), a widely employed herbicide and fungicide. Technical PCP can contain up to 13% impurities, a part of which could consist of residual HCB (7).

HCB has been found mutagenic in S. cerevisiae (Ceppo 632/4 strain) using reversion from histidine and methionine as a measure of the induced mutation (8).

HCB pretreatment of rats has been shown to lead to an increase in liver microsomal 2,4-diaminoanisole to a mutagen after a dose of 10 mg/kg intraperitoneally (9). HCB has recently been reported to induce thyroid tumors and liver hemangioblastomas in Syrian golden hamsters when fed at levels of 50–200 ppm (4–16 mg/kg-day) (10).

HCB was the causative agent in a severe outbreak of porphyrin cutaneatarda symptomatica involving several thousand people in Turkey between 1955 and 1959 (11–13). It was suggested that an intake of 4–16 mg/kg-day of HCB in the above hamster study (10) was within the range of the estimated quantities accidently consumed by the Turkish people for several months at a time, resulting in severe toxic porphyria (13).

Chlorodioxins (polychlorinated dibenzopdioxins) have been the focus of intense investigations, primarily since the disclosure that the highly toxic, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) appeared (at levels ranging from 10 to 30 ppm) in some samples of the herbicide 2,4,5-T (14) and since its teratogenic effects in certain mammals have been reported (14). More recent samples of 2,4,5-T contain 0.5 ppm TCDD (15).

The dioxins found in the contaminated samples of 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and in the chlorophenols are formed during the manufacturing process by condensation of two molecules of 2,4,5-trichlorophenol under conditions of high temperature, high pressure, and alkalinity.

Woolson et al. (16) surveyed the polychlorodibenzo-p-dioxin content in 129 samples of 17 different pesticides derived from chlorophenols. Of these samples, 76% contained less than 0.1 μg/g of TCDD in the technical material, whereas 7% contained more than 0.1 μg/g, and 9% contained more than 10 μg/g of TCDD. While no TCDD was de-
tected in the 20 tri-, tetra-, or pentachlorophenol samples examined, high levels of other dioxins (e.g., hexa-, hepta, and octachlorodibeno-p-dioxins) were found.

In studies of Firestone et al. (17), TCDD was found in three of six samples of 2,4,5-trichlorophenol but was not detected in any of 11 samples of tetra- and pentachlorophenol examined.

Pentachlorophenol and its salts are used in large quantities as herbicides, fungicides, as wood preservatives, and as slimeicides in paper and pulp mills. Plimmer et al. (18) found 17 ppm of the hexa-, 108 ppm of the hepta-, and 144 ppm of octodioxins in technical pentachlorophenol samples. Blaser et al. (19) reported hexachloro- and octachlorodibenzo-p-dioxin at levels of 9–13 ppm and 575–1980 ppm respectively, in four commercial samples of domestically manufactured pentachlorophenol.

The toxicology of chlorinated dibeno-p-dioxins has been reviewed by Schwetz et al. (20). All chlorodibenzo-dioxins are not alike in their mammalian toxicological properties and hence their individual unequivocal identification is vital. TCDD is by far the most toxic of the chlorinated dioxins (20, 21). Recently Van Miller et al. (22) reported the increased incidence of neoplasms in rats exposed to low levels (50 ppb/day) of TCDD. The high incidence of neoplasms in rats fed subacute levels of TCDD suggests the carcinogenic potential of the compound. The tumors of ductal epithelium (e.g., lung, sebaceous gland, and the cholangiosarcomas) are consistent with the findings in nonhuman primate fed TCDD. Van Miller et al. (22) cite the possibility that TCDD is a potent promoter of neoplastic changes rather than an inducer. Neoplasms in the liver, the primary site of TCDD localization (23), were found only in rats fed 1 and 5 ppb TCDD in their diets.

Reports of increased liver cancer in Vietnamese 8 to 10 years following exposure to defoliants containing TCDD (24) tend to support a promotion mechanism for neoplasms caused by TCDD according to Van Miller et al. (22).

DiGiovanni et al. (25) recently reported the tumor-initiating ability of TCDD and the PCB Aroclor 1254 in the two-stage system of mouse skin carcinogenesis.

One area of recent concern involves the finding of nitrosamines as impurities in a variety of herbicides (26–29). These ranged from less than 50 μg/l. to 640,000 μg/l. nitrosamines (e.g., N-nitrosodimethylamine and N-nitrosodipropylamine) (20). It has been estimated that 950 to 1000 pesticide products may contain nitrosamines, and a sizeable number of these pesticides are available for use by homeowners (27). High levels of nitrosamines in soils (believed to arise from the use of triazine herbicides which can combine with nitrogen fertilizer) have been previously reported (30), as well as plant uptake and leaching of dimethylnitrosamine (31).

Zaldivar and Wetterstrand (32) suggest that a positive correlation exists between the use of nitrate fertilizers (leading to enhanced nitrate and nitrite contents of food) and human stomach cancer. Areas with high fertilizer will also be most heavily treated with pesticides according to Seiler (33).

It should also be noted that several commonly used pesticides are derivatives of N-methylcarbamic acid and could conceivably give rise to the corresponding N-nitrosocompounds by interaction with nitrous acid in the environment or in vivo. For example, Carbaryl (N-methyl-1-naphthylcarbamate), a widely used insecticide, can be nitrosated under conditions simulating those of the human stomach (e.g., mild acid, 37°C, in the presence of nitrite) although in relatively low yields (34). The reaction product N-nitrosocarbaryl, structurally related to the known carcinogen nitrosomethyl urethane, has been shown to be a directly acting carcinogen, inducing local sarcomas in rats after subcutaneous injection of a single dose (34) and after administration at doses of 130 mg/kg twice weekly to male Sprague-Dawley rats induced squamous cell carcinoma of the forestomach (35). Lijinsky and Taylor (36) also reported the induction of invasive squamous carcinomas of the stomach in female Spraque-Dawley rats administered a total dose of 0.22 mmole of nitrosocarbaryl by gavage in olive oil solution.

N-Nitrosocarbaryl has also been shown to be a potent mutagen (37–40), inducing base-pair substitution activity in Salmonella typhimurium TA 1535 tester strain at 0.5 μg/plate as well as demonstrating a relatively mild frameshift activity (39) inducing mitotic gene conversion in Saccharomyces cerevisiae (38). Beattie and Kimball (40) reported that mutagenesis induced in H. influenzae by nitrosocarbaryl consists of both replication-dependent and replication-independent components.

Given the chemical structure N-nitrosocarbaryl, Marshal et al. (39) considered the mutagenesis experiments in the Ames assay with TA1535 tester strain to be somewhat predictable. For example, nitrosocarbaryl has a good "leaving group" which could be expected to interact with cellular nucleophiles such as DNA and proteins.

Regan et al. (41) recently reported that in human cells, nitrosocarbaryl is apparently split into aromatic and aliphatic fragments, and the latter (methyl-containing residue) binds irrevocably to human DNA, forming many alkali-labile bonds.

These investigations have been further extended
by Blevins, Lijinsky, and Regan (42) to the effects of the N-nitroso derivatives of six insecticide esters of N-methylcarbamic acid (e.g., aldicarb, baygon, carbofuran, landrin, methomyl, and Bux-ten). Numerous single-strand breaks were apparent in the DNA of all the nitroso derivative-treated human cells but not in the DNA of those treated with the parent insecticides. Since the effect of the nitroso derivatives on the DNA could be observed for at least 20 hr after removal of the chemical from the cultures, the DNA-repairing events normally occurring in human cells after damage initiated by these chemical agents was not repaired in the same way as was UV-type DNA damage or ionizing-type DNA damage in human cells. These observations, (as earlier shown by Regan et al. (41), suggest that human cellular DNA in vivo is irreversibly altered by nitrosated N-methyl carbamate insecticides resulting in numerous alkali sensitive bonds.

Uchiyama et al. (43) demonstrated the mutagenicity of eight nitroso derivatives of N-methyl carbamate insecticides (e.g., 2-sec-butyl-, 2-isopropyl-, 2-isoproxy-, 3,4-xyllyl-, 3,5-xyllyl-, 2-chlorophenyl-, 3-tolyl-) in addition to 1-naphthyl-(carbaryl) utilizing the “Rec-Assay” with Bacillus subtilis, Marbring 45T and 17A and the auxotrophic mutant of E. coli B/r WP-2 try-.

In the rec-assay method, all eight nitrosocarbamates exhibited far stronger DNA damaging potencies than MNNG (N’-nitroso-N-nitrosoguanidine) and most of them were comparable to or more potent than mitomycin-C. The chemical structure characteristic of those derivatives showing extraordinarily high response to rec-assay was considered to be rather massive branched side-chain in the ortho positions of phenyl carbamates, while simple and mono-substituted and chlor derivatives yielded greater induction of back mutations (43).

Seiler (33) recently examined 37 nitrosogas pesticides belonging to the chemical groups of amides, carbamates, and ureas which were nitrosated with sodium nitrite in vitro. The nitrosated compounds were tested for mutagenic activity in the bacterial spot test with S. typhimurium his G46 tester strain. In most cases in which nitrosation was apparent, mutagenicity was also manifest. Over 70% of the tested carbamates gave a positive mutagenicity response, whereas less than 40% of the ureas and only one out of six amides gave a positive response. This might indicate that nitrosated carbamates act as direct mutants, whereas nitrosated ureas containing larger side groups might act preferentially by splitting off nitrosated alkylamines (44) and hence are thus more or less indirect mutants. Those pesticides reacting positively in the bacterial spot test with S. typhimurium his G46 were then fed to mice in combination with sodium nitrite in order to assess the formation and mutagenicity of these nitroso compounds in vivo. With the already known exception of ethylenethiourea (ETU) no pesticide produced enhanced numbers of micronuclei in mouse bone-marrow erythrocytes when fed together with nitrite. Dose-response experiments with intraperitoneal injection on N-nitroso-ETU revealed an apparent no-effect level of about 15–18 mg/kg. Seiler (33) concluded from experiments performed with agricultural chemicals plus sodium nitrite that the danger of mutagenic events stemming from N-nitrosation in vivo could be regarded as small provided that the micronucleus test is a valid indication for the nonmutagenicity of N-nitroso compounds in vivo (which it might not be), and that germ cells are not more susceptible to the damaging action of nitroso compounds that are somatic cells (42), and that the nitrosation in vivo does not proceed to a very much larger extent in man than in the mouse. Two parameters that work in opposite directions are apparently involved: a decreased pH in the human stomach increasing the yield of nitroso compound and smaller absolute and relative amounts of both nitrite and pesticide, lowering the yield of the nitroso derivative.

It is also interesting to note the case of ETU (ethylenethiourea), which is a trace contaminant in a spectrum of fungicidal ethylene bisdithiocarbamates. However, ETU can also arise from mammalian metabolism of these fungicides as well as from cooking dithiocarbamate-treated vegetables. The total amount of ETU ingested by man could be about 0.1 mg/day.

The average nitrite ingestion is in the range of 11-12 mg/day. Assuming a 100% conversion of ETU to nitroso-ETU this would yield a concentration of 2 µg/kg according to Seiler (33).

As has been suggested earlier, residues of pesticides and nitrite in human food may be a health hazard to man, since many pesticides carry secondary and tertiary amino group which are known to form mutagenic and carcinogenic nitroso compounds in the presence of nitrite under conditions resembling those in the human stomach. In contrast, there is a paucity of information regarding the ability of chlorinated pesticides (which contain amino groups differently bound to the molecule) to react with nitrous acid. For example, in the herbicides Pyrazon (1-phenyl-4-amino-5-chloropyridazone) and chlorthiamid (2,6-thiobenzamide) the amino groups are in the α-position to the C=C double bond or to the C=S double bond, respectively. Egert et al. (45) demonstrated the formation of N-methylthiocyanate in 6% yield from the interaction of 10⁻³ M sodium thiocyanate and 10⁻³ M
sodium nitrite at pH 1, whereas chlorthiamid reacts under analogous conditions to the rearrangement product, 2,6-dichloro-N-phenyl isothiocyanate, in a yield of 43%. The above derivatives of Pyrazon and chlorthiamid induced mutations in E. coli K-12 (343/113) in the presence of metabolically active liver microsomes, while the parent pesticides were not mutagenic under any condition (45).

A number of related chlorinated olefinic or ethylenic industrial chemical have been identified as carcinogens and/or mutagens, such as vinyl chloride (CH₂ = CHCl) in experimental animals and man, vinylidene chloride (CH₂ = CCℓ₂) and 2-chlorobutadiene (chloroprene) (CH₂ = CCH = CH₂) in in vitro mutagenicity testing, the latter possibly being carcinogenic in man; trichloroethylene (CICH = CCℓ₂) in intact animal carcinogenicity testing, and in vitro mutagenicity testing (46, 47). It has been postulated that all these compounds are activated in mammalian metabolism to electrophilic epoxides (oxiranes) which very readily react by alkylation with essential cellular macromolecules (46).

Recent work by DeLorenzo and co-workers (48) reveals interesting relations between structure and mutagenic effects of a number of carbamates, herbicides, and fungicides used widely in agriculture. It was found that three thiocarbamate compounds, diallate (I), sulfallate (II), and thiallate (III), were mutagenic in the presence of a liver microsomal function on S. typhimurium strains TA 1535 and TA 100. This indicates that the metabolic products of these thiocarbamates are causing base-pair substitutions. It was postulated that, since the 2-chloroallyl group is common to all three mutagenic compounds but is not common to the 17 non-mutagenic compounds, a metabolic derivative of this group is probably responsible for the mutagenic activity.

```
[CH₃₂CH]-N-C=S-CH₂-C=CHCl
O  I  Cl
(CH₃CH₂₆-N-C=S-CH₂-C=CH₂
S II  Cl
[(CH₃CH₂)N-C=S-CH₂-C=CCℓ₂
O III  Cl
```

It was suggested by DeLorenzo et al. (48) that the thiocarbamates are hydrolyzed at the thioester link- age, releasing the alkyl mercaptan as a first step in metabolism (49). The 2-chloroallyl group is further metabolized and could yield a reactive intermediate analogous to the mutagenic species postulated as an intermediate in the metabolism of vinyl chloride (46). In addition, the 2-chloroallyl group has a chemical structure very similar to compounds related structurally to vinyl chloride (e.g., vinylidene chloride) which has the dichloroethenyl structure found in triallate.

The mutagenicity of triallate and diallate was further recently demonstrated in the monohaploid pelargonium zonale Kleiner Liebling (2n = x = 9); in these cases the mutation rates were 6 to 8 times higher than in the controls (50).

Related to the above studies (48) is the recent finding (51) of mutagenicity of pesticides containing 1,3-dichloropropene (DD soil fumigant and Telone). The active principle of DD soil fumigant and Telone is a mixture of the cis (IV) and trans (V) isomers of 1,3-dichloropropene. Both isomers are mutagenic in Salmonella strains TA 1535 and TA 100. 2,3-Dichloro-1-propene (VI), a minor component of the commercial preparation Telone, was also found to be mutagenic in these tester strains. Mutagenesis of these tests is an indication of a base-pair substitution event causing a missense mutation. DeLorenzo et al. (51) suggested that the mutagenic effects of the isomeric 1,3-dichloropropenes and of some related compound could be compared to the mutagenic effect of vinyl chloride. The structural similarity between these compounds suggesting a similar mechanism of action.

Neudecker et al. (52) recently reconfirmed the mutagenicity of both cis- and trans-isomers of 1,3-dichloropropene in S. typhimurium TA 1535, even without microsomal activation. (The cis isomer was more active than the trans isomer by a factor of about 2.) Surprisingly, not only was there no enhancement, but there was even a marked reduction in the rate of back mutations after addition of microsomes; moreover, the cytotoxicity of both isomers was drastically reduced.

Additional chloro derivatives of mutagenic interest are dichloroacetaldehyde (VIII) and 2,2-dichloro-1,1-dihydroxyethanephosphonic acid methyl ester (VIII), which were formed solvolytically from desmethyltrichlorophene, an in vivo metabolite of the organophosphorus Trichlorophen (IX). Compounds VII and VIII were shown to possess mutagenic activity comparable to that of Trichlorophen in the dominant lethal test in mice at equimolar dosage (53). It was postulated by Fisher et al. (53) that the genetic effects of this pesticide may be due in part to the action of its degradation products (VII, VIII).

The universe of potential mutagenic and/or carcinogenic environmental agents (e.g., pesticides, industrial chemicals, food additives and drugs) is
11. Can, C., and Nigogosyan, G. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. Report of 348 cases caused by this fungicide. J. Am. Med. Assoc., 183: 88 (1963).
12. Courtneay, K. D., et al. Teratogenic evaluation of 2,4,5-T, Science 168: 864 (1970).
13. Helling, C. S., et al. Chlordioxins in pesticides, soils and plants. J. Environ. Qual. 2: 171 (1973).
14. Woolson, E. A., Thomas, R. F., and Ensor, J. Survey of polychlorodibenzo-p-dioxin content in selected pesticides. J. Agr. Food Chem. 20: 351 (1972).
15. Finster, D., et al. Determination of polychlorodibenzo-p-dioxins and related compounds in commercial chlorophenols. J. Assoc. Off. Anal. Chem. 55: 85 (1972).
16. Pimmer, J. R., and Woolson, E. A. Mass spectrometric identification of the hepta- and octa-chlorinated dibenzo-p-dioxins and dibenzofurans in technical pentachlorophenol. J. Agr. Food Chem. 21: 90 (1973).
17. Blaser, W. W., et al. Determination of chlorinated dibenzo-p-dioxins in pentachlorophenol by gas chromatography, mass spectrometry. Anal. Chem. 48: 984 (1976).
18. Schwert, B. A., et al. Toxicology of chlorinated dibenzo-p-dioxins. Environ. Health Perspect. 5: 87 (1973).
19. Miller, R. A., Norris, L. A., and Hawkes, C. L. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxins (TCDD) in aquatic organisms, Environ. Health Perspect. 5: 177 (1973).
20. Van Miller, J. P., Lalich, J. J., and Allan, J. R. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere 10: 625 (1977).
21. Van Miller, J. P., Marlar, R. J., and Allan, J. R. Tissue distribution and excretion of tritiated tetrachlorodibenzo-p-dioxins in non-human primates and rats. Food Cosmet. Toxicol. 14: 31 (1976).
22. Ton That, T., et al. Le cancer primaire du foie au Viet-Nam. Chirurgie 99: 427 (1973).
23. Digiovanni, J., et al. Tumor-initiating ability of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Aroclor 1254 in the two-stage system of mouse skin carcinogenesis. Bull. Environ. Contam. Toxicol. 180: 552 (1977).
24. Anonymous. Nitrosamines found in herbicides, in vivo formation documented. Toxic Materials News 3: 148 (1976).
25. Anonymous. Nitrosamines: EPA refuses suspension request; NIOSH promises alert. Toxic Materials News 3: 156 (1976).
26. Anonymous. Nitrosamines found in commercial pesticides. Chem. Eng. News 54 (2): 33 (1976).
27. Anonymous. EPA investigating nitrosamine impurities in 24 herbicides. Chem. Eng. News 54 (1): 12 (1976).
28. Anonymous. High levels of nitrosamines in soils lead to government task force, Pestic. Chem. News 4: 56 (1976).
29. Dean-Raymond, D., and Alexander, M. Plant uptake and leaching of dimethyl nitrosamine. Nature 262: 394 (1976).
30. Zaldivar, R., and Wetterstrand, W. H. Further studies of a positive correlation between exposure to nitrate fertilizers (NaNO3 and KNO3) and gastric cancer death rates: nitrates and nitrosamines. Experimentia. 31: 1354 (1975).
31. Seiler, J. P. Nitrosation in vitro and in vivo by sodium nitrite, and mutagenicity of nitrogenous pesticides. Mutat. Res. 48: 225 (1977).
32. Eisenbrand, G., Ungerer, O., and Preussmann, R. The reaction of nitrite with pesticides. II. Formulation, chemical properties and carcinogenic activity of the N-nitroso derivative of N-nitroly-naphthyl-carbamate (carbaryl), Food Cosmet. Toxicol. 13: 365 (1975).
33. Eisenbrand, G., Schmahl, D., and Preussmann, R. Carcinogenicity in rats of high oral doses of N-nitroso carbaryl, a nitrosated pesticide. Cancer Letters 1: 281 (1976).
34. Lijinksy, W., and Taylor, H. W. Carcinogenesis in Sprague-Dawley rats of N-nitroso-N-alkyl carbamate esters.

130

Environmental Health Perspectives

enormous. With the recognized limitations of resources both in an economic and scientific sense, it behooves us to more judiciously exercise priorities of agent selection.

The recognition of structural features of pesticides, their metabolic degradation and/or transformation products, and their intrinsic precursor trace impurities to related known mutagens and/or carcinogens should greatly assist in the setting priorities for testing.

REFERENCES

1. Ridgeway, R. L., et al. Pesticide use in agriculture, Environ. Health Perspect. 27: 103 (1978).
2. Seiler, J. P. Evaluation of some pesticides for mutagenicity, Proc. Eur. Soc. Toxicol. 17: 398 (1976).
3. Barthelmess, A. Mutagen Arzneimittel. Arzneimittel-Forsch. 6: 157 (1956).
4. Goldstein, A. J. Mutations, W. J. Scholl, Ed., Univ. of Michigan Press, Ann Arbor, Michigan, 1960, p. 172.
5. IARC. Ortho- and para-dichlorobenzenes. In: Some Anti-Thyroid and Related Substances Nitrofurans and Industrial Chemicals, Vol. 7, International Agency for Research on Cancer, Lyon, 1974, pp. 231–244.
6. Wapensky, L. A. Collaborative study of gas chromatographic and infrared methods for dacthal formulations. J. Assoc. Off. Anal. Chem. 52: 1284 (1969).
7. Melnikov, N. N. Halogen derivatives of some aromatic hydrocarbons, Residue Revs. 36: 67 (1971).
8. Guerzoni, M. E., DelCupolo, L., and Ponti, L. Attività mutagenica degli antiarassitari. Riv. Sci. Tech. Alim. Nutr. Um. 6: 161 (1976).
9. Dybing, E., and Aune, T. Hexachlorobenzene induction of 2,4-diaminoanisole mutagenicity in vitro. Acta Pharmacol. Toxicol. 40: 575 (1977).
10. Cabral, J. R. P., et al. Carcinogenic activity of hexachlorobenzene in hamsters. Nature 269: 510 (1977).
11. Schmid, R. O. Cutaneous porphyria in Turkey. New Engl. J. Med. 263: 397 (1960).
12. Ockner, R. K. and Schmid, R. Acquired porphyria in man and rats to hexachlorobenzene intoxication. Nature 189: 499 (1961).

Environmental Health Perspectives
Cancer Letters 1: 275 (1976).
37. Elespuru, R., Lijinsky, W., and Setlow, J. K. Nitroso carbaryl as a potent mutagen of environmental significance. Nature 247: 386 (1974).
38. Siebert, D., and Eisenbrand, G. Induction of mitotic gene conversion in Saccharomyces cerevisiae by N-nitrosated pesticides. Mutat. Res. 22: 121 (1974).
39. Marshall, T. C., Dorough, H. W., and Swim, H. E. Screening of pesticides for mutagenic potential using Salmonella typhimurium mutants. J. Agr. Food Chem. 24: 560 (1976).
40. Beattie, K. L., and Kimball, R. R. Involvement of DNA replication and repair in mutagenesis of Haemophilus influenzae induction by N-nitrosocarbaryl. Mutat. Res. 24: 105 (1974).
41. Regan, J. D., et al. Nitrosocarbaryl: its effect on human data. Mutat. Res. 38: 293 (1976).
42. Blevins, R. D., Lijinsky, W., and Regan, J. D. Nitrosated methyl carbamate insecticides: effect on the DNA of human cells. Mutat. Res. 44: 1 (1977).
43. Uchiyama, M., et al. The mutagenicity of nitroso derivatives of N-methylcarbamate insecticides in microbiological methods. Bull. Environ. Contam. Toxicol. 14: 389 (1975).
44. Elespuru, R. K., and Lijinsky, W. The formation of carcinogenic nitroso compounds from nitrite and some types of agricultural chemicals. Food Cosmet. Toxicol. 11: 807 (1973).
45. Egert, G., Parlar, H., and Greim, H. Formation of promutagens from the herbicides Pyrazon and Chlorthiamid in the presence of nitrous acid. Mutat. Res. 46: 217 (1977).
46. Bartsch, J., and Montesano, R. Mutagenic and carcinogenic effects of vinyl chloride. Mutat. Res. 32: 93 (1975).
47. Fishbein, L. Potential Industrial Carcinogens and Mutagens. EPA Report 560/5-77-005, Washington, D. C., May 5, 1977.
48. DeLorenzo, F., et al. Mutagenicity of diallate, sulfallate, and triallate and relationship between structure and mutagenic effects of carbamates used widely in agriculture. Cancer Res. 38: 13 (1978).
49. Kaufman, D. D. Degradation of carbamate herbicides in soil. J. Agr. Food Chem. 15: 582 (1967).
50. Pohlheim, E., Pohlheim, F., and Günther, G. Mutagenicity testing of herbicides with a haploid pelargonium. Mutat. Res. 46: 232 (1977).
51. DeLorenzo, F., et al. Mutagenicity of pesticides containing 1,3-dichloropropene. Cancer Res. 37: 1913 (1977).
52. Neudecker, T., Stefani, A., and Henschler, D. In vitro mutagenicity of the soil nematicide 1,3-dichloropropene. Experientia 33: 1084 (1977).
53. Fischer, G. W., Schneider, P., and Schuefler, A. Zur Mutagenität von Dichloracetaldehyde und 2,2-Dichlor-1,1-dihydroxy-äthanphosphonsäuremethylester, möglichen Metaboliten des phosphororganischen Pestizides Trichlorphon. Chem. Biol. Interactions 19: 205 (1977).