Accumulation of Organochlorine Pesticides in Man

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Abstract □ It is generally known that organochlorine pesticides are slowly eliminated and that they accumulate in humans. By using pharmacokinetic relationships, these properties were quantitated to make them more meaningful. Repeated dosing causes the average level of dichlorodiphenyltrichloroethane at equilibrium to rise to 500 times that following a single dose. The degree of accumulation of dieldrin is about three times as great.

Keyphrases □ Organochlorine pesticides—accumulation in man, pharmacokinetic relationships, quantification □ Pesticides, organochlorine—pharmacokinetic relationships used to quantify accumulation in man □ Dichlorodiphenyltrichloroethane—pharmacokinetic relationships used to quantify accumulation in man □ Dieldrin—pharmacokinetic relationships used to quantify accumulation in man

Organochlorine pesticides have been used for many years, and today they represent an integral part of the environment. The realization that these compounds have become usual components of various animal species, including man, has prompted investigations into the toxicology, distribution, and metabolism of dichlorodiphenyltrichloroethane (commonly known as DDT) and other so-called persistent pesticides. A recent review by Robinson (1) summarized the pertinent literature. Although it is known that these substances tend to accumulate in man, the degree of accumulation has not been quantitated.

METHOD

This problem of accumulation is conveniently approached from the viewpoint of pharmacokinetics. The time dependence of the amount of pesticide in the body, A_B, is given by:

$$\frac{dA_B}{dt} = \frac{dA_A}{dt} - \frac{dA_E}{dt} \qquad \text{(Eq. 1)}$$

where dA_A/dt is the rate of absorption, and dA_E/dt is the rate of elimination. After repeated dosing, an equilibrium state is attained, in which the average plasma concentration during a dosage interval and, presumably, A_B remain constant. Under these conditions, $dA_B/dt = 0$ and Eq. 1 may be rearranged to:

$$\frac{dA_E}{dt} = \frac{dA_A}{dt} \qquad \text{(Eq. 2)}$$

Elimination is usually a first-order process (2) given by the relationship:

$$\frac{dA_E}{dt} = KA_B \qquad \text{(Eq. 3)}$$

where K represents the elimination rate constant. Equation 3 has been demonstrated to hold for the pesticide dieldrin (3). If the dose of pesticide remains constant, the average absorption rate at equilibrium is constant. By taking this into account, Eqs. 2 and 3 may be combined to give:

$$K = \frac{I}{A_B} \qquad \text{(Eq. 4)}$$

in which I is the (constant) average rate of absorption.

The degree of accumulation R may be calculated using the definition of Wagner (4):

$$R = \frac{\bar{C}_\infty}{\bar{C}_1} \qquad \text{(Eq. 5)}$$

where $\bar{C}_\infty$ is the average blood concentration at equilibrium (after repeated dosing), and $\bar{C}_1$ is the average blood concentration after a single dose. Unfortunately, the blood values needed to calculate the degree of accumulation of organochlorine pesticides are not available. In fact, $\bar{C}_1$ can *never* be determined in our world because there is probably not a single human being free of these pesticides. However, we may perform the calculation by evaluating average blood levels analytically; $\bar{C}_\infty$ is a function of the dose D, the fraction absorbed F, the volume of distribution V, the elimination rate constant, and time between doses τ (5):

$$\bar{C}_\infty = \frac{FD}{VK\tau} \qquad \text{(Eq. 6)}$$

Equations 5 and 6 are model independent if elimination occurs from the central compartment. Equation 6 assumes that the elimination rate constant does not increase with multiple dosing as a result of self-stimulation of metabolizing enzymes. $\bar{C}_1$ depends on the same parameters as does $\bar{C}_\infty$ and, in addition, the absorption rate constant k (6):

$$\bar{C}_1 = \frac{FD}{V\tau}\left(\frac{k}{k-K}\right)\left[\frac{1-e^{-K\tau}}{K} - \frac{1-e^{-k\tau}}{k}\right] \qquad \text{(Eq. 7)}$$

If the elimination rate constant is much smaller than the absorption rate constant (this is certainly true of the organochlorine pesticides), Eq. 7 reduces to:

$$\bar{C}_1 = \frac{FD}{VK\tau}(1 - e^{-K\tau}) \qquad \text{(Eq. 8)}$$

Substituting Eqs. 6 and 8 into Eq. 5, one arrives at the result:

$$R = \frac{1}{1 - e^{-K\tau}} \qquad \text{(Eq. 9)}$$

The elimination rate constant is related to the biological half-life $t_{1/2}$ by the equation:

$$K = \frac{0.693}{t_{1/2}} \qquad \text{(Eq. 10)}$$

so that R may be expressed in terms of the biological half-life:

$$R = 1/1 - e^{\left[\frac{-(0.693)(\tau)}{t_{1/2}}\right]} \qquad \text{(Eq. 11)}$$

RESULTS AND DISCUSSION

Biological half-lives of the materials under consideration are shown in Table I. The value for dieldrin was taken from the literature (3). The half-life of dichlorodiphenyltrichloroethane was calculated from Eqs. 4 and 10, using the data of Table VI, *Reference 7*.

Table I—Accumulation of Organochlorine Pesticides in Humans

Substance	Biological Half-Life, Days	Degree of Accumulation, R
Dieldrin	369	1600
Dichlorodiphenyltrichloroethane	115	500

The average daily dose of dichlorodiphenyltrichloroethane, 3.7 mg. (3.5 mg. given in the feeding study + 0.2 mg., the average daily intake in food), was substituted for I in Eq. 4. The assumption was thus tacitly made that all of the administered pesticide was actually absorbed. The mean content of pesticide found in body fat, 613 mg., was taken to represent the body total, since other work showed that over 95% of body dichlorodiphenyltrichloroethane is dissolved in the fat (8).

To estimate the degree of accumulation of pesticides in the general population, it was assumed that administration occurs with meals, three times a day. R was calculated by Eq. 11, using a value of 1/3 day for τ and the values for $t_{1/2}$ given in Table I. The values of R, also shown in Table I, indicate that the degree of accumulation of the organochlorine pesticides is indeed high. In the case of dieldrin, for example, repeated dosing causes the average body level to rise to 1600 times the value that would result after a single dose.

The pesticides treated in this study have been widely used in agriculture. Although toxic effects have not been demonstrated in volunteers receiving doses many times higher than those to which the general population is at present exposed, the safety of these chemicals in humans is still open to question. Organochlorine pesticides have been shown to elicit pharmacological effects in animals and are blamed for decreases in the population of several species, including the bald eagle. In a sense, widespread use of persistent pesticides represents an uncontrolled experiment on man and other animals. The extremely long half-lives of these materials and their consequent accumulation in man, coupled with their slow degradation in the environment, make us extremely vulnerable if it should turn out that they are not as safe in man as their proponents would have us believe.

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p-Substituted 1,2-Diphenylindolizines as Anti-Inflammatory Agents

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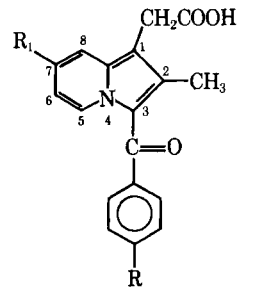
Abstract □ In an effort to explore indolizines as potential medicinal agents, some *p*-substituted 1,2-diphenylindolizines were prepared. These compounds were designed to be investigated for possible anti-inflammatory activity. The syntheses were accomplished *via* the Chichibabin–Stepanow synthesis, using the properly substituted benzylpyridines and phenacyl bromides.

Keyphrases □ 1,2-Diphenylindolizines, *p*-substituted—synthesized and screened as potential anti-inflammatory agents □ Anti-inflammatory agents, potential—synthesis of *p*-substituted 1,2-diphenylindolizines, pharmacological screening □ Indolizines, *p*-substituted 1,2-diphenyl—synthesized and screened as potential anti-inflammatory agents

Considerable interest in the fundamental chemistry of the indolizine heterocyclic system has been generated by the publications of Boekelheide and coworkers (1–4). In contrast to the study of this aspect of the indolizine system, there have been only scattered reports of the biological activity of indolizines and no systematic study has been reported (5–7). Buu-Hoï and Xuong (8) considered 2-(4-fluoro-2-methylphenyl)indolizine and 2-(4-fluoro-2-methylphenyl)-7-methylindolizine as carcinogens, but they failed to mention whether these compounds were actually tested for carcinogenic properties. Buu-Hoï *et al.* (9) reported that 2-(4-cyclohexylphenyl)-indolizine was noncarcinogenic when painted on the skin of experimental animals.

Carbon and Brehm (10) considered 1-indolizinealanine as a tryptophan antimetabolite. Cardellini *et al.* (11) reported that, in preliminary tests, indolizine-1-



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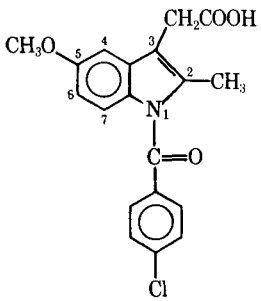

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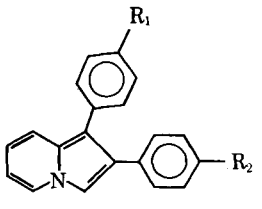

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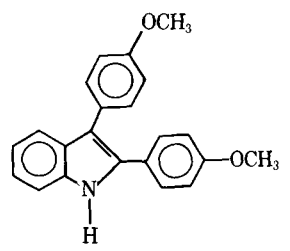

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