Metabolism of 4-Dimethylamino-3,5-Xylyl Methylcarbamate (Mexacarbate, Active Ingredient of Zectran® Insecticide): A Unified Picture

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ZECTRAN® insecticide (4-dimethylamino-3,5-xylyl methylcarbamate, mexacarbate) is a very effective, broad-spectrum insecticide belonging to the methylcarbamate group of pesticides (FREEMAN, et al. 1967; GEORGHIOU and METCALF 1962; HARDING 1961; KENAGA, et al. 1962; METCALF 1961; O'BRIEN and MATTHYSSE 1961; SHOREY, et al. 1962).

Safe and efficient use of this insecticide requires an understanding of its fate in the environment. Toward this end, a considerable body of information regarding its decomposition in living organisms has accumulated in the literature. This review brings the information together in such a way as to present a unified picture of the flow of reactions by which the insecticide is converted to other compounds in these biological systems.

The facts concerning decomposition of mexacarbate in biological systems are shown in Table I. Perusal of this information suggests that the biochemical reactions involved in decomposition of this compound are much the same in all biological systems studies. The identified reaction products do not differ significantly whether found in plants, animals, insects, soils, or as a result of *in vitro* use of enzyme systems.

A variety of different reactions are postulated to take place based on the identity of mexacarbate metabolites which have been characterized: oxidative N-demethylation, deamination, hydrolysis, and conjugation. N-demethylation of the compound and certain of its metabolites yields compounds D, E, F, G, and H. The aromatic amino group can be replaced with a hydroxyl group as evidenced by the presence of HQ as one of the metabolites. DMAX and HQ can only be formed as a result of hydrolysis of the carbamate functional group. Water-soluble metabolites of the insecticide are always present. Available evidence (KUHR and CASIDA 1967; MEIKLE 1972; WILLIAMS, et al. 1964a,b) indicates that these are, for the most part,

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TABLE I

Identified Metabolites Arising From Metabolism of Mexacarbate

Compound	Compound[a] Designation	Source and[b] Reference
4-Formamido-3,5-xylyl methylcarbamate	D	P(ABDEL-WAHAB, et al. 1966), I(ROBERTS, et al. 1969), E_I(TSUKAMOTO and CASIDA 1967)
4-Methylformamido-3,5-xylyl methylcarbamate	E	P(ABDEL-WAHAB, et al. 1966), I(ROBERTS, et al. 1969), E_I(TSUKAMOTO and CASIDA 1967), E_A(OONNITHAN and CASIDA 1966,1968) S(LASKOWSKI 1972)
4-Amino-3,5-xylyl methylcarbamate	F	P(ABDEL-WAHAB, et al. 1966), I(ROBERTS, et al. 1969), E_I(TSUKAMOTO and CASIDA 1967), E_A(OONNITHAN and CASIDA 1966,1968) S(LASKOWSKI 1972)
4-Methylamino-3,5-xylyl methylcarbamate	G	P(ABDEL-WAHAB, et al. 1966), I(ROBERTS, et al. 1969; MISKUS, et al. 1969), E_I(TSUKAMOTO and CASIDA 1967), E_A(ONNITHAN and CASIDA 1966, 1968), S(LASKOWSKI 1972)

Compound	Compound[a] Designation	Source and[b] Reference
4-Dimethylamino-3,5-xylyl N-hydroxymethylcarbamate	H	P(ABDEL-WAHAB, et al. 1966), E_I(TSUKAMOTO and CASIDA 1967), E_A(OONNITHAN and CASIDA 1966,1968)
2,6-Dimethylhydroquinone	HQ	P(WILLIAMS, et al. 1964a), A(WILLIAMS, et al. 1964b), S(LASKOWSKI 1972)
2,6-Dimethylhydroquinone conjugate	HQ-C	A(WILLIAMS, et al. 1964b), P(WILLIAMS, et al. 1964a)
4-Dimethylamino-3,5-xylenol	DMAX	P(WILLIAMS, et al. 1964a), A(MISKUS, et al. 1969; WILLIAMS, et al. 1964b), S(LASKOWSKI 1972)
-Dimethylamino-3,5-xylenol conjugate	DMAX-C	A(WILLIAMS, et al. 1964b), P(WILLIAMS, et al. 1964a)
4-Methylamino-3,5-xylenol conjugate	MAX-C	P(MEIKLE 1972)
4-Amino-3,5-xylenol	AX	S(LASKOWSKI 1972)
4-Amino-3,5-xylenol conjugate	AX-C	P(MEIKLE 1972)

[a]The first five designations are the same as those used by ABDEL-WAHAB, et al. (1966) and by OONNITHAN and CASIDA (1968).

[b]P = plants; A = animals; I = insects; S = Soil, E_A = rat liver microsomes, E_I = $NADPH_2$-requiring enzyme system from housefly abdomen.

conjugates of hydroxylated compounds; in some cases, the carbamate group is intact and, in other cases, only the phenol portion of the molecule in involved. Indications are that the rate-limiting reaction must be hydroxylation of N-methyl groups and/or hydrolysis of the carbamate functional group rather than conjugate formation because unconjugated hydroxylation and hydrolysis products are present only in small amounts if at all (KUHR and CASIDA 1967). In the case of soil, the scarcity of 3,5-xylenol derivatives suggests that, once formed, these compounds undergo ring-opening rather rapidly (LASKOWSKI 1972).

Figure I is the proposed, unified pathway for mexacarbate metabolism in plants, animals, insects, and soils. Compounds in brackets have not been identified, but rather their existence is assumed because they are necessary intermediates in the overall reaction scheme.

All possible conjugates have not been included in the figure. However, any compound containing a hydroxyl or unsubstituted amino group is a potential candidate for conjugate formation. In this respect, KUHR and CASIDA (1967) found five water-soluble conjugates from bean plants, all with their carbamate group intact. Note that the initial attack on the insecticide involves two reactions, both of which are oxidative N-demethylations. These are competing reactions and, without exception, attack on the N-dimethylamino functional group proceeds most rapidly. This is expected because the dimethylamino group has a higher "effective concentration" of N-methyl groups than does the carbamate portion of the molecule.

Metabolism in Plants. The degradation pattern for mexacarbate in plants (beans, broccoli, corn, soybeans) appears to proceed initially in both directions (Figure I). The fact that every identified metabolite (Table I) has been found in plants is strong evidence in support of this proposal. DMAX and its glycoside are generally found in substantially smaller quantity that the combined total of other metabolic products (MEIKLE 1972; WILLIAMS, et al. 1964a,b). Again, this indicates that N-demethylation of the dimethylamino group is the predominant reaction. The flow of compounds toward HQ is relentless and is diverted only when N-demethylation and subsequent hydrolysis of the carbamate functional group lead to 3,5-xylenol derivatives. In general, these substances and the end-product of this reaction, HQ, are transported in an inactivated state to the regions of active secondary growth. They are eventually transformed to lignin and other polymolecular ergastic substances of the cell wall and materials extraneous to the cell wall. Here they are permanently stored and effectively isolated from regions of active growth.

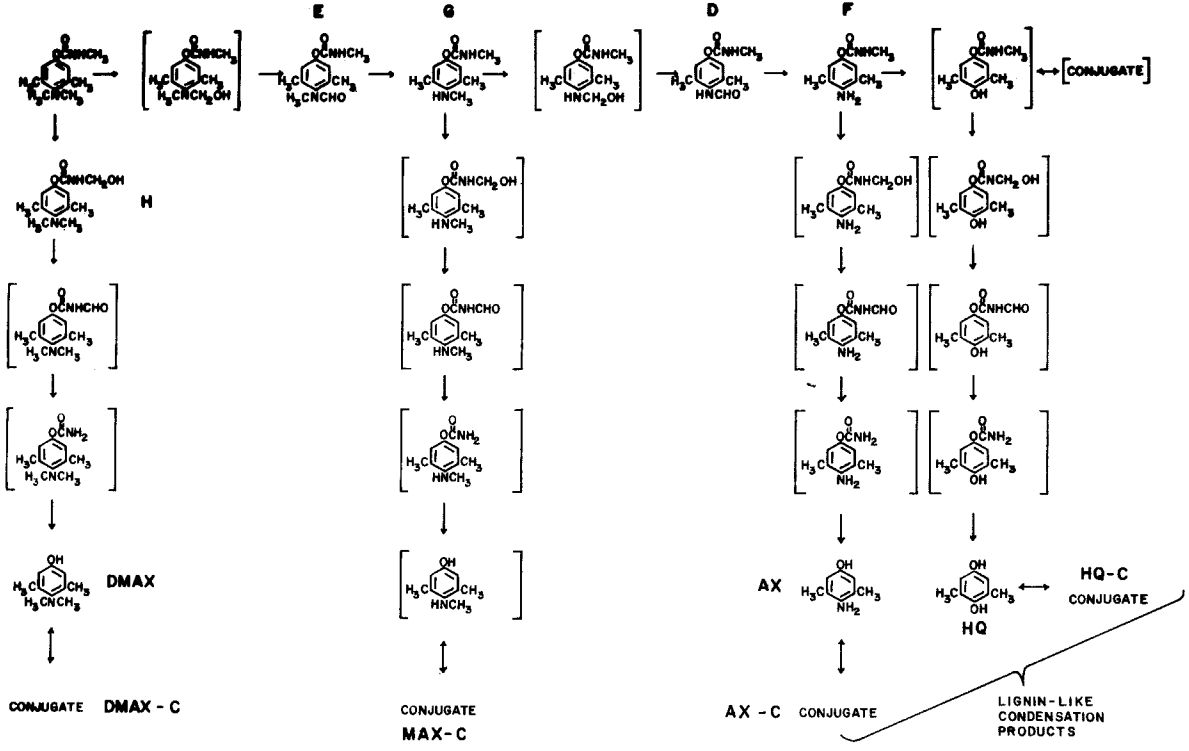

Figure 1 - Proposed unified pathway for mexacarbate in plants, animals, soils and insects. Compounds in brackets have not been identified.

Animal Metabolism. Animals possess well-defined organs for the excretion of metabolic products. Foreign compounds enter the body mostly by absorption from the gastrointestinal tract and are taken via the portal vein to the liver where they are converted to compounds which are generally more polar and less lipid-soluble. These products are then excreted in the bile to be voided in the feces, or are taken into the kidneys and excreted in the urine.

There are also secondary sites of reaction located in other tissues, such as the lungs, the gastrointestinal tract, the kidneys, and the skin. Studies with rat liver microsomes (OONNITHAN and CASIDA 1966, 1968), in which compounds E, F, G, and H have been identified, indicate that the metabolic pathway for mexacarbate degradation in animals proceeds very much the same as with plants (Figure I). The similarity is also emphasized by work with animal urine (dogs, mice) (MISKUS, et al. 1969; WILLIAMS, et al. 1964b) where the only compounds identified have been HQ and DMAX, almost entirely as conjugates. These compounds arise as a results of the operation of both competing reactions shown in Figure I.

Insect Metabolism. Using the $NADPH_2$-requiring enzyme system from the housefly abdomen, mexacarbate was degraded to compounds D, E, F, G, and H (TABLE I) (TSUKAMOTO and CASIDA 1967). These facts support the proposal that, as with plants and animals, the metabolic pathway for degradation of this insecticide in insects proceeds as shown in Figure I. Results from studies with intact insects (spruce budworm, tobacco budworm, housefly), however, only partially support this scheme (ROBERTS, et al. 1969; MISKUS, et al. 1969)--compound H has not been found. What this means is that the metabolic pathway involving N-demethylation of the 4-dimethylamino group predominates. No HQ or DMAX was found in any of the insect studies. This suggests that any or all of these compounds, possibly as conjugates, were rapidly excreted, thus allowing essentially no build-up to occur within the insects.

Metabolism in Soil. Three substances tend to accumulate in soil as a result of mexacarbate metabolism: compounds G, DMAX, and HQ (LASKOWSKI 1972). Again, this information tends to confirm the reaction scheme shown in Figure I. However, in the case of decomposition by soil microorganisms, there is a modification to the scheme not shown: N-demethylation and ring-opening reactions can occur with DMAX and other 3,5-xylenols. The distribution of products as a result of these two competing reactions is a matter of rate phenomena. This

added complexity does not exist for plants, animals, and insects because these organisms conjugate the xylenols very rapidly, thus effectively inactivating the compounds.

The seemingly great number of metabolic products shown in Figure I for the breakdown of mexacarbate are, in fact, largely intermediates on their way to only a very few end-products. When we study the impact of this insecticide on the environment, the search for metabolites becomes much simpler because these intermediates are never present in high concentrations and are relatively shortlived.

In conclusion, the relatively modest amount of information available concerning the metabolism of mexacarbate in several biological systems, along with a knowledge of permissable enzymatic reactions, has allowed the construction of a unified reaction scheme which is consistent with the facts. The scheme explains the gradual flow of metabolites into a pool of water-soluble compounds and ultimately, in the case of plants, into the polymeric ergastic substances of the cell wall (lignin) and the materials extraneous to the cell wall (tanin, etc.). This relentless process serves as a waste disposal system and allows the organism to maintain its state of health in the face of potentially toxic substances.

References

ABDEL-WAHAB, A. M., KUHR, R. J., and CASIDA, J. E., J. Agr. Food Chem. 14, 290 (1966).

FREEMAN, T. N., STEHR, G. W., HARVEY, G. T., and CAMPBELL, I. M., Can. J. Entomol. 99, 499 (1967).

GEORGHIOU, G. P. and METCALF, R. L., J. Econ. Entomol. 55, 125 (1962).

HARDING, J. A., J. Econ. Entomol. 54, 1254 (1961).

KENAGA, E. E., DOTY, A. E., and HARDY, J. L., J. Econ. Entomol. 55, 466 (1962).

KUHR, R. J., and CASIDA, J. E., J. Agr. Food Chem. 15, 814 (1967).

LASKOWSKI, D. A. (Dow Chemical U.S.A., Walnut Creek, Calif.), unpublished work (1972).

MEIKLE, R. W. (Dow Chemical U.S.A., Walnut Creek, Calif.), unpublished work (1972).

METCALF, R. L., Agr. Chem. 16, No. 6, 20 (1961).

MISKUS, R. P., ANDREWS, T. L., and LOOK, M., J. Agr. Food Chem. 17, 842 (1969).

O'BRIEN, R. D. and MATTHYSSE, J. G., Agr. Chem. 16, No. 11, 28 (1961).

OONNITHAN, E. S., and CASIDA, J. E., Bull. Environ. Contam. Toxicol. 1, 59 (1966).

OONNITHAN, E. S., and CASIDA, J. E., J. Agr. Food Chem. 16, 28 (1968).

ROBERTS, R. B., MISKUS, R. P., DUCKLES, C. K., and SAKAI, T. T., J. Agr. Food Chem. 17, 107 (1969).

SHOREY, H. H., REYNOLDS, H. T., and ANDERSON, L. D., J. Econ. Entomol. 55, 5 (1962).

TSUKAMOTO, M., and CASIDA, J. E., Nature 213, 49 (1967).

WILLIAMS, E. A., MEIKLE, R. W., and REDEMANN, C. T., J. Agr. Food Chem. 12, 453a, 457b (1964).