Journal of the Minnesota Academy of Science

Volume 50 | Number 3 Article 5

1984

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Chemicals Used in Personal Mosquito Control (A Review)

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ABSTRACT — The use of chemicals in personal mosquito control is summarized. The historical developments in chemical control agents are traced from essential oils to synthetic organic materials. Structure-activity relationships (SAR) are discussed, and the implications of SAR approaches in the development of future personal mosquito repellents are explored.

Historical Review

The use of plants and plant extracts by man to provide protection against biting insects and a variety of insect-borne diseases is well documented in the literature (1). By 1930 a variety of essential oils such as pennyroyal, clove, nutmeg, juniper berry, wintergreen, and various pine oils had found use as personal mosquito repellents (2). Oil of citronella, which provided about four hours of protection (3), was one of the most widely used at this time.

During the 10 to 15 years prior to 1940, some efforts were made to identify more effective and cosmetically acceptable personal insect repellents (4). Several synthetic organic compounds were identified as insect repellents during this period. Three synthetics: dimethyl phthalate; butyl 3, 4-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylate (Indalone™), and 2-ethyl-1, 3-hexanediol (Rutgers 612) were formulated to provide a standard all-purpose personal insect repellent for the military. This formulation did not provide adequate protection. In response to this need, a major screening effort to identify insect repellents was begun by the United States government.

Beginning in 1942, this effort was launched at the Orlando, Florida, laboratory of the Bureau of Entomology and Plant Quarantine. Some sense of the magnitude of this effort is seen by reviewing two United States Department of Agriculture publications (5, 6) which describe this screening program. During this period, approximately 20,000 materials were evaluated.

Several materials were identified as potential insect repellents. As an example, an early formulation, M-2020 (7), for skin applications consisted of dimethyl phthalate, Rutgers 612, and dimethyl *cis*-bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylate (dimethyl carbate). This formulation provided about two hours of protection against the anopheline mosquito and about four hours against ticks and chiggars. The repellent N, N-diethyl-*meta*-toluamide (DEET), first synthesized by McCabe et al. (8), was also evaluated in this program (5). Since 1955, this material has gained wide acceptance as a mosquito repellent. DEET has been sold under more than 20 trade names in the United States (9).

The need for repellents exhibiting characteristics such as improved residual activity, broader efficacy against a variety of insects (including biting flies), improved cosmetic qualities, and minimal plasticizing action, has resulted in a sustained research and development effort in this area (10). Our labortory has patented a family of nitrogen-oxygen heterocyclics (11, 12) as broad-spectrum insect repellents. One of these materials, 3-acetyl-2-[2,6-dimethyl-5-heptenyl] oxazolidine, (Citronyl™) is registered in both Canada and Australia for skin application and was successfully put into commercial production. This compound was formulated in personal repellent products in both these countries. Recent studies on this material have shown it to be a broad-spectrum mosquito repellent (13) and to be repellent to non-biting flies (14) and the chiggar mite (15).

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Structure-Activity Relationships

Massive screening programs and selective synthetic efforts, based in part on analogy with known insect repellent structures, have been primarily responsible for identifying new insect repellents. We still, however, do not understand why specific chemicals repel insects. Such knowledge would assist in the development of more effective insect repellent chemicals.

A survey of chemical structures reported to possess insect repellent activity illustrates an immense structural and functional diversity. Specific structural or functional moieties that contribute to repellent activity are, therefore, difficult to identify.

This situation is made more clear by examination of standard bioassay protocols (16) used to evaluate mosquito repellency. Test data is generally expressed as a duration of repellent protection and is generated on both cloth and skin. Other test procedures determine a minimum effective dose below which a test compound no longer prevents biting. A large selection of variables that affect test data are associated with these test protocols (10).

The design of bioassay protocols that will minimize the effects of testing variables is a critical first step in the systematic study of personal mosquito repellents. A variety of statistical approaches (17) are now available with which to analyze bioassay data and to indirectly provide an increased undertanding of the mode-of-action of insect repellents. Efforts to identify and quantify important physicochemical variables which affect mosquito repellency have met with limited success over the last 50 years.

Boiling Point

Since mosquito repellents are assumed to produce an olfactory sensation, boiling point was one of the first physicochemical factors to be investigated in the study of repellents (18). In this early study, Bunker and Hirschfelder observed that repellents normally had boiling points in excess of 150°C. However, early investigators also noted that molecular structural factors, in addition to boiling point, influenced repellency. Dethier (2) thought there was evidence to indicate a relationship between repellency and boiling point as well as between repellency and the degree of oxygenation in the test materials.

Specific structural series have been shown to exhibit residual repellency dependent upon the boiling points of members of the series. Roadhouse (19) found that an optimum boiling point range was 230°C to 260°C for a series of 1, 2, glycols. However, even within this restricted series, slight changes in structure resulted in significant changes in repellent activity. 2-Methyl-1-phenyl-1,2-propanediol and 1-methyl-1-phenyl-1,2-propanediol exhibit essentially identical boiling points. However, the 1-methyl isomer is repellent and the 2-methyl isomer is inactive. A similiar observation was made with 4,6,6-trimethyl-1,2-heptanediol and 1-methyl-1-phenyl-1,2-propanediol. Both compounds have similar boiling points and carbon numbers but exhibit large differences in repellent activity.

A series of ring-substituted N,N-diethylbenzamide analogues of DEET were investigated by Johnson (20). The boiling point maximum that still permitted repellency was 120°C C/0.5 mmHg. Garson (2) reported an analysis of test data generated by Alexander and Beroza (21) on a series of aliphatic amides of cyclic amines. A plot of repellency versus boiling point gave a bell-shaped curve. Useful repellent compounds exhibited a boiling point range of 110°C to 140°C /0.5 mmHg.

Partition Coefficient

The partition coefficient has been the most frequently employed parameter for structure-activity studies in biochemical systems (22). The type of partition coefficient generally used describes the distribution of a material between adjacent hydrophilic and lipophilic liquid phases.

Limited studies attempting to relate this physicochemical parameter to mosquito repellency have been carried out. No correlation between partition coefficient and repellency was found in a study of N,N-diethylbenzamides (20). In this study, mosquito repellency was expressed as a duration of protection on human skin. Compounds which do exhibit repellency were oberved to have both lipid and water solubilities (19, 20).

An early study by Dethier and Chadwich (23) on contact repellents with blowflies (*Phormia regina*) examined the correlation between partition coefficient and intrinsic repellency. Dethier's work measured instrinsic repellency; known concentrations of materials were bathing the chemoreceptor sites of the blowfly. This study demonstrated that the mean concentration at the threshold of rejection for a series of alcohols decreased as the distribution coefficient betweeen water and cottonseed oil at 25°C decreased.

Additional Physicochemical Factors

Both molecular weight (24) and surface tension (2) have been investigated as factors in mosquito repellency. Since boiling point exhibits some colinearity with molecular weight and surface tension, the significance of these factors in repellency is uncertain at this time.

Models of Repellent Action

Although our understanding of how chemicals repel mosquitoes is quite limited, several factors which attract mosquitoes to a host have been identified (25). Such information may be used to construct models of repellent action. These models are based on the hypothesis that a repellent acts to inhibit an attractant response by the mosquito to the host. Factors in human skin identified as attractive to mosquitoes are odor, carbon dioxide, heat, moisture, and warm-moist convection currents.

Odor

Lysine and alanine (26), L-lactic acid (27), and sex hormones (28) are among several components isolated from skin and reputed to be attractive to mosquitoes (29). It was once thought that appropriate analogues of lactic acid might block the lactic acid-sensing mechanism and thus act as repellents (10). This approach did not lead to materials possessing high intrinsic activity. Recent work by Davis and Sokolove (30) describes the identification of a pair of chemoreceptor neurons of the mosquito (*Aedes aegypti*) which are sensitive to lactic acid. The repellent DEET was shown to inhibit both lactic acid-sensitive neurons.

Carbon Dioxide

The role of carbon dioxide in host attraction by the mosquito is still unclear. Some workers consider carbon dioxide an attractant since it is used in mosquito traps for population samplings (31). Gillies (32), however, observed that a directional response is lacking when carbon dioxide is used as a source. Several reports (25) describe the action of carbon dioxide on mosquitoes as activation. These inconsiste

results may be caused by differences in bioassay technique (16).

Limited work on a model of repellent action based on carbon dioxide activation was carried out by Kashin (33). This study involved the hypothesis that gamma-aminobutyric acid (GABA) might be inhibitory to neurophysiological pathways involving carbon dioxide sensing. Reaction of GABA with carbon dioxide would produce a glutamic acid-like compound that would be excitatory to these pathways.

Heat and Moisture

The combination of heat and moisture is well documented as an effective, short-range mosquito attractant (25). Carbon dioxide is reported to be a necessary component in initiating this attractant response (34).

Water vapor and carbon dioxide receptors have been identified on the antennae of *Aedes aegypti* (35). McIver (36) recently proposed a model for the action of DEET on *Aedes aegypti.* In locating a host, which is mediated by olfactory cues, DEET is proposed to interact with the lipids of the olfactory dendritic membranes in such a way as to alter the normal response to attractants.

Future Directions in Repellent Research

Emphasis will be placed on developing bioassay protocols that generate meaningful intrinsic repellency data. Such data, and the general availability of sophisticated statistical analysis software packages, will greatly facilitate the study of quantitative structure-activity relationships for insect repellents. With the consequent identification of factors that influence intrinsic repellency as an information base, a variety of improved insect repellent products may be developed. Such developments may include highly effective area repellents, systemic repellents, and synergists for existing repellents.

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