Agriculture Canada

September 19, 1984 T-1-245

FOOD PRODUCTION AND INSPECTION BRANCH	DIRECTION GÉNÉRALE, PRODUCTION ET INSPECTION DES ALIMENTS	SECTION PESTICIDES

TRADE MEMORANDUM

RE: Guidelines for Developing a Pesticide Toxicologv Data Base

The purpose of this memorandum is to provide registrants of pesticides and other interested groups and agencies with a final format of the guidelines for pesticide toxicology data requirements that were previously distributed for comment as memorandum R-1-211. dated October 30, 1981.

The need for definitive toxicology data guidelines for pesticide registration has been repeatedly expressed in various quarters including provincial regulatory agencies and pesticide manufacturers. To meet this need, the Pesticides Division of Agriculture Canada has worked cooperatively with colleagues in the Health Protection Branch of Health and Welfare Canada to develop guidelines which reflect the types of tests generally needed in delineating the toxicity of a pesticide and its potential hazards to humans.

The attached guidelines were circulated as memorandum R-1-211 and have benefited from constructive review by provincial health officials and representatives of the pesticide manufacturing industry. Meetings were also held in which the proposed guidelines were discussed in detail.

It is not the intent of these guidelines to delineate data requirements, and registrants are encouraged to discuss the proposed testing program for their specific products with appropriate officers in Health and Welfare Canada to ensure that suitable tests are selected.

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Director
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Encl.
Distribution: KP, KQ, KR, N5, PP, PW, PX, all registrants

HEALTH PROTECTION BRANCH
GENERAL GUIDELINES FOR DEVELOPING A PESTICIDE TOXICOLOGY DATA BASE

Summary

The Health Protection Branch's mandate with respect to pesticides involves the assessment of health hazards from residues in food and from occupational and bystander exposure, resulting from proposed new or extended uses and existing uses of pesticides.

In the area of pesticide residues in food, the Health Protection Branch administers the Food and Drug Regulations. Any pesticide which is used on food or may contaminate food in any way must be evaluated by the Food Directorate to determine the nature, levels and toxicity of such residues and to determine the residue limits which may be necessary under the Food and Drug Regulations.

In the case of occupational or bystander health hazards, the Health Protection Branch advises other agencies, particularly Agriculture Canada who administer the Pest Control Products Act. Any pesticide which is sold or used in Canada must be evaluated by the Environmental Health Directorate to determine the possible hazards to people exposed occupationally or inadvertently (bystanders).

In order to evaluate new pesticides, new uses of existing pesticides and to re-evaluate presently used pesticides, extensive data are needed by both the Food Directorate and the Environmental Health Directorate. The attached guidelines for pesticide toxicology data are intended to assist applicants in selecting the type of toxicity tests, the results of which would be essential to the evaluations of pesticide hazards. It should be noted, however, that the Health Protection Branch considers that the applicant is responsible for proving the safety of any pesticide they wish to use or sell in Canada. The applicant is also responsible for discussing detailed data requirements for specific chemicals with Health Protection Branch officials.

These guidelines should not be construed as inflexible requirements but rather as an outline of the types of tests generally needed in delineating the toxicity of a chemical and the potential hazards to humans. It is conceivable that some of the tests and species listed might he unwarranted for certain products, and the Health Protection Branch reserves the right to request alternate or additional toxicity studies if considered to be necessary.

It is not the intention in these guidelines to detail protocols for tests. Applicants should therefore consult protocols developed and published by various agencies including the Health Protection Branch of Health and Welfare Canada, the Environmental Protection Agency in the U.S.A., the World Health Organization, and Organization for Economic Cooperation and Development (OECD). However, it is recommended that proposed protocols be discussed with HPB officials prior to the initiation of the toxicity studies since there may be aspects of some tests which are specific for Canadian registration.

Data Organization

Trade Memoranda T-1-237 and T-1-239, dated October 1, 1983 issued by Agriculture Canada outline the format for organizing all data in pesticide submissions together with the required distribution of copies. It should be noted that the Health Protection Branch requires data on all aspects outlined in these Trade Memoranda, except for efficacy data, although the guidelines referred to herein relate only to toxicology data requirements.

The following should be read in conjunction with the attached Tables 1 to 4. Please note that although suggested species are shown in the tables, the use of other species should be discussed with HPS officials.

Test Substance

Under most circumstances, the test substances will be the technical grade of the active ingredient that is produced during the normal manufacturing process. Under certain circumstances, it may be required that an analytically pure grade of the active ingredient, an inert ingredient ot the formulation, a contaminant or impurity, a metabolite or degradation product, or any combination of these be tested. Some tests, as outlined below, must be conducted on the formulation.

Acute Toxicity Studies

Most of these studies define the dosage and range of a single or multiple administration of the pesticide within a 24-hour period or less which is lethal within a specified post-treatment observation period. The data from these studies, as well as the results from dermal irritation, eye irritation and dermal sensitization studies are used to identify the relative acute toxicity of the product for classification and for label precautionary statements. Preliminary information may also be obtained on the specific toxic effects and the mode of action of the test product.

Whenever appropriate, no observed effect levels (NOEL) with respect to specific signs of poisoning should also be reported because this information is useful in estimating the potential hazards from acute exposure. Regularly scheduled observations for signs of toxicity should be made, noting time of onset and duration. Particular attention should be given to the selection of appropriate test materials, e.g., technical grade material or active ingredients or formulation.

Short Term Studies

These studies delineate the toxic potential of the pesticide through continuous or daily repeated administration for less than one sixth of the lifespan of the test species. The data obtained are useful in elucidating such problems as possible cumulative action, variation in species sensitivity and in identifying specific organ effects. They also provide guidance for the selection of dosages for chronic studies.

Since the 90-day oral study has been widely used, it is suggested that this be done for purposes of comparison only with the technical material. However, to evaluate the potential hazard of a product to workers or bystanders, consideration should be given to conducting dermal and/or inhalation studies with both the technical and formulated product. The duration of these studies and the appropriate route of exposure should be determined after the results from the pharmacokinetic studies are evaluated. Also the use

pattern and physical properties of the product will assist in determining the appropriate studies. Consideration should also be given to including a recovery study in at least one of the 90-day studies with the technical material.

Long Term Studies

These studies provide information on the maximum dosage level which produces no discernable injury to animals, and on the tumorigenic potential of a pesticide when administered continuously or daily over the major portion of the life span of the test animals, and may reveal effects which are not predictable from short term toxicity studies.

Unless data from the other studies indicate otherwise, the long term studies should be conducted using the technical grade of the active ingredient administered by the oral route.

SPECIAL STUDIES

(i) Pharmacokinetic Studies:

A good understanding of the pharmacokinetics of the pesticide will enable more-judicious selection of appropriate routes of administration and dose levels in long term studies, and actual tests which should be done on a product. Since one of the purposes of such studies is to aid in the extrapolation of animal toxicity data to man, studies in multiple animal models are usually required. The variability of test material absorption by different routes of administration should be considered as well as what may constitute an appropriate medium for dissolving test materials. Distribution of test material in a biological system and tissue fluids, as well as analytical methodology should be considered in planninq pharmacokinetic studies.

(ii) Mutagenicity Tests:

These tests may be used as a screen for mutagenic potential as well as a pre-screen for carcinogenic potential. The limitations of these tests are realized, but they provide useful information which can be used along with the results from the whole animal experiments to give some preliminary indication of the mutagenic and carcinogenic potential of the test product.

(iii) Studies of Breakdown Products:

Toxicity studies on metabolic and environment breakdown products may be necessary to evaluate the potential hazards of human exposure to such chemicals in food, and in treated areas which must be entered by workers and bystanders.

(iv) Teratogenicity Studies:

These studies should be conducted in two species and should provide data on the potential of pesticides to produce or alter the incidence of congenital malformations.

(v) Reproduction Studies:

These studies provide information on the potential effects the pesticides might have on the reproductive capacities of the parental generation from mating through lactation and on the offspring from conception through lactation and matinq. vhe study should be conducted on one ("a") litter from each of two generations unless postnatal adverse effects, doubtful effects on any reproductive parameter, or, lack of stabilization of blood and tissue levels (cumulative compound) are observed. Then, "b" litters will be required in at least 1 generation.

(vi) Exposure Studies:

These studies should be conducted only after there is reasonable assuredness that the applicator will not be placed at undue risk and could coincide with efficacy field trials. These studies will be used to determine the magnitude of the margin of safety under use conditions. Appropriate protocols for such studies should be determined in consultation with Health Protection Branch officials.

Dated: August 1984
Health Protection Branch
Health and Welfare Canada

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