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Characteristics of the U.S. EPA's Office of Pesticide Programs' Toxicity Information Databases

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The United States Environmental Protection Agency's Office of Pesticide Programs (OPP) requires that data from toxicity testing be submitted to the OPP to support the registration of pesticide chemicals. Once the toxicity data are submitted, they are entered into various toxicity databases. The studies are listed in an archival database to catalog and allow retrieval of the study for review. Reviews of toxicity studies are then placed into a separate database that can be retrieved to support a regulatory position. Toxicity information for health effects other than cancer and gene mutations from chronic exposure is reviewed through a reference dose (RfD) approach, and these decisions and supporting data are entered into an RfD database. Carcinogenicity data are reviewed by a peer review process, and these decisions are entered into a newly developed database to show the regulatory decision with supporting data. The mutagenicity data are reviewed and acceptable data are entered into the Genetic Activity Profile system to catalog and display the submitted information. These databases contain the information used for hazard evaluations as part of the OPP review of pesticide chemicals.

Introduction

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), first enacted in 1947 and most recently amended in 1988, provides for the registration of pesticides with the United States government. The United States Environmental Protection Agency (EPA), and, in particular, the EPA's Office of Pesticide Programs (OPP), is charged with administering FIFRA. Furthermore, the EPA makes in-depth assessments to determine if there are unreasonable adverse health effects associated with a pesticide. To support a registration of a pesticide and to assess if there are unreasonable adverse effects, the EPA requires a wide spectrum of toxicity information for submission to the OPP for review.

The types of toxicity information required for submission to the OPP are detailed in the Part 158 (Data Requirements for Registration) of the Code of Federal Regulations (*1*). Table 1 provides a list of some of the types of toxicity information required for submission. The OPP's Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals [first published in 1982 (*2*); periodic updates are performed] provides guidance on how to implement the Part 158 requirements.

Table 1. List of some of the types of toxicity information required for submission to the U.S. Environmental Protection Agency's Office of Pesticide Programs.[a]

Acute testing	Oral, dermal, eye irritation
Subchronic testing	90-day feeding studies, neurotoxicity
Chronic testing	Chronic feeding, carcinogenicity
Special testing	Metabolism, dermal penetration
Reproduction and developmental testing	
Mutagenicity testing	

[a]Toxicology data requirements under part 158 (*1*).

Once toxicity information is submitted to the OPP, it is tracked through the different divisions of the OPP. It is logged into tracking databases (which will not be discussed here) and sent to scientists for review. Once the reviews are completed, the information is then loaded into the various toxicity databases developed within and for the OPP. This paper gives some characteristics of these toxicity information databases in the OPP. It should be noted that many of the databases within the OPP are not mature, smoothly running databases, and many are still in the state of development, particularly the genotoxicity and carcinogenicity databases. However, because the information in these databases on pesticide chemicals in many instances are unique, and because pesticides are important environmental chemicals, these databases contain an excellent source of material that is useful for hazard evaluation. In the future, the role these databases play in hazard evaluation will increase in importance as they enlarge and mature.

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Pesticide Document Management System

Once a toxicity study is submitted to the OPP, the document is recorded into the Pesticide Document Management System (PDMS). The PDMS is used to manage all centrally held documents of archival significance to the OPP. The on-line PDMS index is a computer database that provides a complete bibliographic citation for each of the toxicity studies submitted to the OPP. As a document such as a toxicity study is entered into the system, it is assigned a master record identifier (MRID) number. This unique number can then be used to catalog the study and to allow subsequent retrieval of the study. For studies submitted to the OPP earlier than the mid-1980s, an accession number was also assigned to many submission packages. The accession number, however, may be assigned to many documents if those documents were submitted at the same time under one submission cover. The MRID number is therefore the preferred identifier because of its unique character; however, the database is searchable by both the MRID and accession numbers. The PDMS database is important, as it contains all the technical information considered by OPP scientists in their reviews.

One-Liners Database

After a study has been submitted, logged into PDMS, and tracked, a scientific review of the study is performed. The reviewed information is captured in a Data Evaluation Report (DER). The DER is the formal record of the OPP's reviewing scientist's review and opinion of that study. In each DER, the results of the study are discussed and a classification regarding acceptability for regulatory purposes (referred to as core grade) is rendered. Once a DER is generated for a study, the information in the DER is entered into the "one-liners" database. This database provides a brief summary of the results of each reviewed study and the study's core grade classification. A document number is assigned to each review that identifies it in the central file system that holds all the reviews. The one-liners database is searchable by study type, test compound, and document number.

The one-liners database is the main toxicity database of reviewed information in the OPP. It contains references via the document numbers to all the reviews performed on every pesticide. This includes any study submitted for review, whether it is acceptable or less than adequate for regulatory purposes. The document number provides a unique identifier for each review, which facilitates acquisition of the review. Also in the one-liners database are the MRID and/or accession numbers, which also facilitate acquisition of the actual study. All this information is accessible via freedom of information requests except for material that is confidential business information (e.g., product formulations).

Once a study has been loaded into the one-liners database, the toxicity information from each study and its review are used for various regulatory decisions and processes, including establishing a reference dose, classifying for carcinogenicity, and assessing potential genotoxicity and heritable risk. All these processes and end points involve, or will involve, a toxicity database to summarize the acceptable material.

Reference Dose Approach and Integrated Risk Information System

The reference dose (RfD) approach is the EPA's principal approach for assessing risk for health effects other than cancer and gene mutations from chronic chemical exposure (*3*). This approach examines the risk and its potential magnitude associated with systemic toxicity. The RfD is a benchmark dose operationally derived from the NOAEL (no-observed-adverse-effect level) by consistent application of uncertainty and modifying factors. Studies such as rat and dog chronic studies and reproduction and developmental studies are used in determining the RfD. The RfD is useful as a reference point for determining the likelihood of adverse effects towards humans; i.e., doses less than the RfD are less likely to be associated with adverse effects, and doses higher than the RfD are increasingly likely to produce adverse effects.

Once an RfD is established, this decision and its supporting information is loaded into two databases. The OPP maintains its own RfD database with the information relevant to the decisions rendered by OPP scientists. It also reflects any subsequent EPA decisions. This information is available via formal request to the OPP. Furthermore, once the OPP makes its decision on the RfD for a pesticide, that decision is brought to the Agency's RfD work group for an Agency-wide decision. Once this group makes its decision, that information is loaded into the Agency's Integrated Risk Information System (IRIS) (*4*).

IRIS, created by the EPA, is an on-line database containing the health risk and EPA regulatory information on specific chemicals. Although designed for EPA staff, it is accessible to outside organizations. Information in IRIS is intended for use in protecting public health through risk assessment and risk management. IRIS is a tool that provides hazard identification and dose–response assessment information. The information contains input from the reference dose work group (discussed above) and the Carcinogen Risk Assessment Verification Endeavor work group (discussed below).

Peer Review Process, Carcinogenicity Classification, and Related Databases

Within the OPP's Health Effects Division (HED), a carcinogenicity Peer Review Committee has been established to determine a weight-of-evidence classification for carcinogenic potential of pesticide chemicals. The committee is composed of selected EPA senior toxicologists whose task is to critically review the evidence for carcinogenicity. This review is performed in accordance with the EPA's Carcinogen Risk Assessment Guidelines (*5*). Once the Peer Review Committee makes a final decision on the carcinogenicity classification, the data, supporting information, and decision factors are loaded into several databases.

The first database is simply a file system where the salient features of each carcinogenicity study for each peer-reviewed chemical is codified. This database provides quick reference to information concerning each study, e.g., species and strain, study duration, dose levels, tumor sites and types, and tumor incidence. It also provides a quick index of the positive and negative acceptable mutagenicity studies that have been submit-

ted to the OPP in association with that chemical. This database is a listing of the carcinogenicity studies and results for the peer-review chemicals and is presented in a manner similar to that for the National Toxicology Program's carcinogenicity information (*6*). Currently there are about 100 peer-review chemicals that have carcinogenicity information extracted from associated studies.

The carcinogenicity information is also loaded into a computerized database that is currently under development. This database will be much more extensive than the one mentioned above. This database will provide actual dose–response data for each study, supporting information such as from dose-setting studies, historical control information, other relevant non-neoplastic effects, structure–activity relationship information, and pharmacokinetics. In addition, the database will provide rationale for the carcinogenicity classification as well as some tracking information for regulatory action. Each piece of information will be searchable. A prototype computerized framework has been set up, but this database is not totally functional at this time.

After the OPP establishes its position on the carcinogenicity of a pesticide chemical and provides a classification, this decision is then presented to the Agency's Carcinogen Risk Assessment Verification Endeavor (CRAVE) work group. The CRAVE provides an Agency-wide consensus on the carcinogenicity assessment of chemicals of concern to the Agency, including pesticide chemicals. The deliberations and decisions from the CRAVE are loaded onto IRIS. The carcinogenicity assessments involve the qualitative weight-of-the-evidence judgment (classification) and a quantitative assessment, if performed, which includes a slope factor and unit risks. This information is designed to supply hazard identification and dose-response assessments concerning the carcinogenicity data.

Office of Pesticide Programs Mutagenicity Data: Genetic Activity Profiles

The mutagenicity data submitted to the OPP are currently being cataloged and characterized in Genetic Activity Profiles. These profiles provide a computerized database that incorporates the qualitative and quantitative data from the mutagenicity studies performed with that pesticide chemical. The profile permits a direct visual assessment of the responses obtained with all the mutagenicity studies and facilitates a computer-based comparison of genetic activity for purposes of chemical selection and structure–activity relationship model development (*7,8*).

The profiles contain only the acceptable studies used to support a pesticide registration, as indicated in the one-liners database. The profile is kept separate from the published literature and International Agency for Research on Cancer profiles but can be merged with them when an examination of the whole spectrum of genetic toxicology information is desired. Additional benefits of the profile methodology include identification of data gaps for the required mutagenicity tests necessary for registration and the use of pattern matching among chemicals with similar structures for structure–activity relationship analyses. Also, the bibliographies generated from the computerized profile database will provide information useful for acquisition of the reviews and submitted mutagenicity studies, except for confidential business information, through the freedom of information process.

There are currently about 60 chemicals with information extracted from their associated mutagenicity studies to be loaded into the Genetic Activity Profiles. There are 600 to 700 pesticidal active ingredient chemicals with registrations that are supported with the OPP. Therefore, this extraction and database support effort will be an ongoing activity that is currently in its beginning stages.

Initial Analysis of Carcinogenicity and Genotoxicity Databases

Because the establishment and entry of the OPP carcinogenicity and genotoxicity information into computerized databases is only in its infancy, any type of detailed, in-depth analyses have been currently precluded. It is the intention of the OPP to conduct such analyses once the information has been cataloged and put into a form amenable for analysis. In the interim, some crude, initial analyses are presented here.

There are 85 chemicals that have a carcinogenicity classification proposed by the OPP Peer Review Committee based on the weight-of-the-evidence for each chemical. Of these 85, 19 are categorized as group B2 chemicals (probable human carcinogen; B2 indicates sufficient evidence in animals and inadequate or no evidence in humans); 49 are group C chemicals (possible human carcinogen); 10 are group D chemicals (not classifiable as to human carcinogenicity); and 7 are group E chemicals (evidence of noncarcinogenicity for humans). It must be kept in mind that the peer review chemicals are a biased group of chemicals because they are selected for peer review based upon an initial review that suggested some evidence for carcinogenic potential. It is hoped that this effort will be expanded to include all pesticides that have long-term bioassays that do not suggest carcinogenic potential. This would help reduce some of the bias inherent with the peer review chemicals for future analysis. Another caveat must be kept in mind for the entire pesticide chemical toxicity database: these chemicals, for the most part, are intended to be biologically active. Therefore, they are an inherently biased group of compounds with which to perform carcinogenicity and genotoxicity correlation analyses.

Of the many mutagenicity test types submitted to the OPP, this analysis will discuss the Salmonella, mouse lymphoma, and Chinese hamster ovary (CHO) (and V79) gene mutation assays, the *in vitro* and *in vivo* cytogenetics assays, the micronucleus assay and the unscheduled DNA synthesis (UDS) assay. A total of 58 (of the 85, peer-review chemicals) compounds have been examined. There are 47 acceptable Salmonella assays of which 42 are negative. The 5 positive results are with compounds that have evidence for carcinogenicity (3 B2 and 2 C group compounds). Of the 42 negative results, 33 chemicals are classified as group B2 or C compounds. There are 20 acceptable mouse lymphoma assays, of which 12 are positive and 8 negative. Eight of the 12 positives and all 8 negatives are compounds that have evidence for carcinogenicity (4 B2 and 12 C group compounds). There are 9 acceptable CHO (or V79) gene mutation assays, of which 7 are negative and 2 are positive. The 2 positives and 5 of the 7 negatives are compounds with evidence for carcinogenicity.

For the *in vitro* cytogenetics assays (CHO, V79, and human lymphocytes), there are 18 acceptable studies. Five of the 7 positives and 10 of the 11 negatives are compounds with evidence for carcinogenicity (3 B2 and 12 C group compounds). Sixteen *in vivo* cytogenetic assays are acceptable, with 14 negative and 2 positive results. Nine of the 14 negatives and both positives are chemicals that have carcinogenicity evidence. There are 19 acceptable studies with acceptable micronucleus assays. Only 1 compound has a positive result, but this is a very weak, statistical positive probably due to a low background. Of the 19 compounds, 17 are associated with evidence for carcinogenicity.

Of the 58 peer-review chemicals examined here, 30 have acceptable UDS studies. All compounds were negative in this assay. Twenty-four of the 30 chemicals have evidence for carcinogenicity. Twelve of these compounds induced liver tumors and were tested for UDS using hepatic cells; there were no positive results even for compounds that induced liver tumors.

We realize that this type of initial analysis only serves to stimulate more questions than answers. It is these additional myriad questions that make this effort interesting, worthwhile, and one that the OPP desires to pursue.

This manuscript has been reviewed by the Office of Pesticides and Toxic Substances and the Health Effects Research Laboratory, U.S. Environmental Protection Agency and approved for publication. Approval does not signify that the contents necessarily reflect the views or policies of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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