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Human Study Submissions to the Office of Pesticide Programs

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Context: Data Submissions to the Office of Pesticide Programs

Pesticides are among the most thoroughly studied substances, and EPA's Office of Pesticide Programs has and exercises strong authority to require submission of data about them. Under the authorities of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act of 1996, OPP has defined many types of studies required to support pesticide registrations and food residue tolerances. A full battery of required tests for a new food-use pesticide might include 200 or more studies, depending on the pesticide's characteristics and use patterns.

OPP receives about one thousand new studies a month–the great majority of them in response to requirements, but some submitted voluntarily in the belief that they will further the agency's understanding of specific pesticides. The historical statistics reported here reflect only studies submitted since January 1, 1990. That date roughly corresponds to the beginning of the era of the Common Rule, and provides a long enough period of study to permit confident identification of current patterns of submission of human studies. Table 1 shows how the human studies received during this period compare to the total flow of new studies into OPP.

Table 1
Study Submissions to OPP 1/1/90 through 8/31/98

Study Type	Number	Percent Total
Studies with Human Subjects	342	0.3%
All Toxicology/Safety Studies	34,000	32.4%
All Studies	105,000	100.0%

Distribution of Human Studies by Type and Purpose

The total figure for human studies includes many different kinds of studies, performed and submitted for very different reasons. Among the important distinctions to be made among these studies are whether exposure of the subjects to pesticides was intentional or unintentional, and among those studies with intentional exposure, whether the purpose of the study was to assess exposure to the pesticide, to assess effects of the pesticide, or some other purpose. Table 2 describes the distribution of these 342 studies in terms of the study types discussed below.

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Table 2 Distribution by Type: Human Studies Submitted to OPP from 1/1/90 through 8/31/98		
Type of Study	**Number**	**% Total**
Studies without intentional exposure	**23**	**6.7%**
Reports of [no] hypersensitivity incidents	16	
Incident follow-up/epidemiological studies[1]	7	
Studies with intentional exposure	**319**	**93.3%**
Studies of exposure	**209**	**61.1%**
Pesticide applicator/mixer/loader exposure	101	
Post-application exposure		
Re-entering field workers	42	
Swimmers	1	
Golfers/lawns/turf	9	
Indoor re-entry	23	
Production worker exposure	26	
Studies of effects	**103**	**30.1%**
Skin patch/wash: irritation or sensitization	64	
Eye irritation	3	
Odor threshold	2	
Metabolism/pharmacokinetics/absorption	26	
NOAEL	8	
Therapeutic drug treatment	**7**	**2.0%**
All human studies	**342**	**100.0%**

[1] In addition, since June 1992 OPP has received reports of over 15,000 incidents involving human exposure to pesticides.

Reports of [no] hypersensitivity incidents are responses to a guideline requirement applicable to biological pesticides. These studies are typically brief, anecdotal reports to the effect that during research and pilot production with the biological pesticide there have been no cases of hypersensitivity. All 16 submitted within the period of this survey were negative.

Most reports of incidents involving pesticides are not submitted to OPP as studies, but as

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incident reports as required under FIFRA section 6(a)(2). A few follow-up investigations, however, have been submitted as studies, and they are shown in the table, combined with a handful of epidemiological studies also submitted during the survey period.

Over 93% of all human studies submitted in the survey period involved intentional exposure of test subjects, but within this category there are important distinctions to be made. First, more than two-thirds of these studies are of exposure rather than of effects. For many years OPP has routinely required exposure studies for applicators, mixers, and loaders of pesticides, and for people re-entering treated areas; some 84% of the exposure studies were directly responsive to these guideline data requirements. These studies are used in occupational and residential risk assessment, and typically involve human subjects performing actions or tasks they would normally perform, while wearing gauze patches or body suits to collect pesticide residues for analysis. The remaining exposure studies were of production workers, and lie on the border between intentional exposure and epidemiological studies.

Tests of pesticide effects in human subjects are also of several distinct types. By far the most frequently submitted are skin patch or skin wash tests for irritation or sensitization potential. These studies typically involve exposure to household or personal use products intended for topical application to human skin, such as insect repellants or anti-microbial cleaning products. Although testing with human subjects is never required, these studies have often been submitted and accepted in place of–not as supplements to–guideline-responsive studies using animal subjects.

Three tests of eye irritation were submitted during the survey period. One was a published report from 1969 concerning an inert ingredient in a pesticide; the other two were studies with a household cleaning product.

Another important category of effects studies addresses rates of absorption, pharmacokinetics, or metabolism in humans. These studies are often precursors to exposure studies, and clarify what to look for as a marker of exposure, or establish rates of dermal absorption.

The final category of effects studies identified in the survey are studies for the purpose of establishing human no-observed-adverse-effect levels, or NOAELs. Eight such studies were submitted during the survey period, involving five different pesticides.

The last two percent of the human studies submitted during the survey period were published reports of therapeutic treatment with materials which are both drugs and pesticides.

Reporting of Ethical Conditions of Testing

The 103 studies in the survey period involving intentional exposure to humans for the purpose of defining effects or NOAELs were reviewed further to determine whether and how they reported the ethical conditions of testing. Several broad patterns were apparent:

- Ethical considerations are more likely to be addressed in more recent studies than in older studies, especially for published studies. Many of the published studies submitted during the

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survey period had been published many years earlier, and were entirely silent on ethical issues.

- Compliance with ethical standards is typically asserted in a summary statement that the study was performed consistent with the Declaration of Helsinki, US Food and Drug Administration rules, or with OECD or other rules. The same laboratory or investigator typically made this assertion in identical language in every report. In no case was the US EPA Common Rule cited

- When informed consent was discussed it was common to include a copy of the consent form. This, too, was typically in standard language for each laboratory or investigator.

- References to an Institutional Review Board were more common in protocols than in reports of the study conduct. In other words, the protocol promised IRB review, but the study did not report that it actually occurred.

- No study report included any discussion of ethical issues considered by an Institutional Review Board.

Table 3 summarizes how issues of ethical conduct were reported for each category of the 90 unpublished effects studies included in the survey. Published studies were excluded from this table because they so seldom addressed ethical questions at all. A failure to report on ethical conduct does not, of course, mean in itself that a study was not conducted ethically; but it does mean that EPA has no basis on which to judge whether the study was conducted ethically.

Table 3
Unpublished Human Studies of Effects: Protection of Human Subjects

Type of Study	No of Studies	Foreign	Avg N	References in Study Report					
				Volunteer Subjects	Informed Consent	IRB	Decl. of Helsinki	FDA Regs	EPA Regs
Skin patch or wash	56	3 (5%)	88	56 (100%)	51 (91%)	11 (20%)	0 (0%)	28 (50%)	0 (0%)
Eye irritation	2	0 (0%)	15	2 (100%)	2 (100%)	2 (100%)	0 (0%)	2 (100%)	0 (0%)
Metabolism/absorption/ pharmacokinetics	23	17 (74%)	6	23 (100%)	19 (83%)	13 (57%)	13 (57%)	9 (39%)	0 (0%)
Odor threshold	1	0 (0%)	38	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)
NOAEL	8	7 (88%)	16	8 (100%)	8 (100%)	8 (100%)	8 (100%)	1 (13%)	0 (0%)
Totals	**90**	**25 (28%)**	**n/a**	**90 (100%)**	**81 (90%)**	**35 (39%)**	**22 (24%)**	**40 (44%)**	**0 (0%)**

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