

**ECONOMIC ANALYSIS OF PROPOSED RULE:  
PROTECTIONS FOR HUMAN RESEARCH PARTICIPANTS**

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## **1 Executive Summary**

The Common Rule as promulgated by EPA (40 CFR Part 26) has guided human subject studies conducted or supported by EPA since it took effect in 1991. The U.S. Environmental Protection Agency (EPA) is proposing to extend the requirements of the Common Rule to all third-party intentional dosing studies intended for submission to EPA under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) or the Federal Food, Drug and Cosmetic Act (FFDCA). The Agency is also proposing to promulgate rules containing the additional protections for special populations adopted by the Department of Health and Human Services (HHS) in 45 CFR Part 46, Subpart B (pregnant women, fetuses, and certain neonates), and Subpart D (children) for human studies not involving intentional dosing exposure. The proposed rule would categorically prohibit any intentional dosing studies for pesticides involving pregnant women and children as subjects. This document evaluates the potential benefits and costs expected to result from the proposed rule.

Scientific research with human subjects has provided a great deal of valuable information to help characterize and control risks to public health. However, the use of such data has also raised particular ethical concerns for the welfare of the human participants as well as scientific issues related to the role of such research in assessing risks. The public has long debated the circumstances under which it should be considered ethical to use humans as human subjects in research, and when it would be appropriate for the government to rely on the results of ethically problematic research.

The Agency currently reviews the ethical aspects of the third-party studies involving intentional human exposure on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide. For human studies involving intentional dosing exposure, most third-party researchers are currently complying with the Common Rule, including subparts B & D, or with the guidelines widely accepted in the international research community such as the Declaration of Helsinki (5).

For human studies not involving intentional dosing exposure, the Agency is not currently requiring third parties to submit information pertaining to the ethical conduct of completed human studies. Third parties are not required to comply with the Common Rule for such human studies, although many are generally responsive to the EPA's guideline requirements which often refer to the Common Rule. The economic analysis focuses on the cost and benefits to industry and the Agency associated with human studies performed after publication of the rule. Using the current practice as the baseline for estimating the potential impact of the proposed rule, the incremental costs and benefits were analyzed for the four options. The cost and benefit of each option are:

### **Option 1**

Option 1 is no change to the current practice. There will be no incremental cost or benefit to industry or the Agency.

## **Option 2**

Option 2 is to extend the requirements of the Common Rule only to third-party studies involving intentional human exposure to identify or quantify toxic effects, and intended for submission to EPA under FIFRA or FFDCa and to prohibit third parties (and EPA) from conducting such studies with pregnant women or children. Researchers intending to conduct human studies covered by the rule would also be required to submit protocols for EPA's review prior to initiating the research. The annual average number of third-party studies involving intentional human exposure to identify or quantify toxic effects, and intended for submission to EPA under FIFRA or FFDCa was estimated to be 14. Under this option, industry will incur incremental annual costs of \$8K, while the Agency will incur incremental annual costs of \$221K.

This option will benefit the affected entities including research subjects, third parties, the Agency, and the public. There would be limited direct benefits of the proposed rule to human study participants including vulnerable populations. Most, if not all, third-party researchers conducting intentional exposure studies are currently following the Common Rule. EPA expects only a small percentage of future intentional exposure studies (and the volunteers in those studies) to be affected. To the extent researchers are not following the Common Rule, the proposed rule would result in greater protections for human subjects, and as a consequence should reduce their risk of harm. The benefits of the proposed rule to third parties will derive from their better understanding of what standards will be applied in the future during the Agency's review process, which will then lead to a more efficient process in preparing submissions to EPA.

The main benefits of the proposed rule to the Agency would come through clarification of the standards to be applied to third-party human research considered by the Agency, which might result in savings in costs associated with case-specific decision-making. Extending the requirements of the Common Rule to research by third parties will also provide some assurance for the public that newly conducted third-party human studies considered by EPA in its regulatory decision-making will be scientifically sound and ethically acceptable, which should result in greater public confidence in and acceptance of EPA decisions.

Further, the Agency's review of the study protocols prior to human studies are initiated will provide an added layer of protection to human subjects. For the third parties, it will also increase the likelihood that the studies are scientifically sound and ethically acceptable under EPA's standards when they are completed. The Agency's ability to make sound regulatory decisions will be enhanced. It will also provide additional assurance for the public that the third-party human studies are conducted in such a way to meet high scientific and ethical standards and used as input to the regulatory decision-making process.

## **Option 3**

Option 3, which reflects the rule being proposed by EPA, is to extend the requirements of the Common Rule to all third-party intentional dosing studies intended for submission to EPA under FIFRA or FFDCa and to prohibit third parties (and EPA) from conducting such studies

with pregnant women or children. Researchers intending to conduct human studies covered by the rule would also be required to submit protocols for EPA's review prior to initiating the research. The annual average number of third-party studies involving intentional human exposure intended for submission to EPA under FIFRA or FFDCA was estimated to be 30. Under this option, the incremental costs were estimated to be \$16K to industry, and \$328K to the Agency.

As explained under Option 2, this option will benefit the affected entities including human subjects, third parties, the Agency, and the public. Since options 2 and 3 involve the same substantive standards, the benefits under both options will be qualitatively the same. However, Option 3 is not confined only to third-party intentional exposures studies to identify or quantify toxic effects, and intended for submission to EPA under the authority of FIFRA or FFDCA. Since this category of human research is greater than the research described for Option 2, the benefits of Option 3 will be quantitatively greater than for Option 2.

#### **Option 4**

Option 4 is to extend the requirements of the Common Rule to all third-party studies intended for submission to EPA under the authority of FIFRA or FFDCA and to prohibit third parties (and EPA) from conducting such studies with pregnant women or children. Researchers intending to conduct human studies covered by the rule would also be required to submit protocols for EPA's review prior to initiating the research. The annual average number of third-party studies intended for submission to EPA under FIFRA or FFDCA was estimated to be 62. Under this option, the annual incremental costs were estimated to be \$203K-243K to industry, and \$601K to the Agency.

Like Option 2 and 3, this option will benefit the affected entities including human subjects, third parties, the Agency, and the public. Option 4 is not confined only to third-party intentional exposures studies intended for submission to EPA under the authority of FIFRA or FFDCA. Therefore, the benefits of Option 4 will be quantitatively greater than for Option 2 and 3.

Impacts on small entities are minimal because the ratio between the cost of complying with the proposed Human Protection Subjects rule and the small entities sales revenue (average \$24 million) is very negligible.

## **2 Background**

Over the years, scientific research with human subjects has provided a great deal of valuable information to help characterize and control risks to public health, but the use of such data has also raised particular ethical concerns for the welfare of the human subjects as well as scientific issues related to the role of such research in assessing risks. Society has responded to the ethical concerns by defining general standards for conducting human research. In the United States, the National Commission for the Protection of Human Subjects of Biomedical and

Behavioral Research issued the Belmont Report titled “Ethical Principles and Guidelines for the Protection of Human Subjects of Research” in 1979.

For most federal agencies in the United States, the principles of the Belmont Report are implemented through the Common Rule, which was developed cooperatively by 17 departments and agencies, including EPA. The Common Rule, as promulgated by EPA (40 CFR Part 26), has guided human research conducted or supported by EPA since it took effect in 1991. In 1978, 1983, and 2001 the Department of Health and Human Services (or its predecessor) adopted rules establishing additional protections for human subjects who are members of special populations.<sup>1</sup>

More broadly, the international medical research community has developed and maintains ethical standards documented in the Declaration of Helsinki, revised several times since it was first issued by the World Medical Association in 1964. These standards apply to research on matters relating to the diagnosis and treatment of human disease, and to research that adds to understanding of the causes of disease and the biological mechanisms that explain the relationships between human exposures to environmental agents and diseases.

Much of the human subject research supporting EPA’s actions is conducted by the research community without direct participation or support by the U.S. government. Although data from human studies have contributed to assessments and decisions in most EPA programs in the past, issues about consideration of and reliance on third-party human research studies have arisen most frequently, but not exclusively, with respect to pesticides.

Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA may require pesticide companies to conduct studies with human subjects, for example, to measure potential exposure to pesticide users or to workers and others who re-enter areas treated with pesticides, or to evaluate the effectiveness of pesticide products intended to repel insects or other pests from human skin. In addition, EPA sometimes encourages other research with human subjects including tests of the potential for some pesticides—generally those designed for prolonged contact with human skin—to irritate or sensitize human skin, and tests of the metabolic fate of pesticides in the human body. These latter studies typically precede monitoring studies of agricultural workers and others to protect them from exposure to potentially dangerous levels of pesticide residues.

In addition to these kinds of research which have been required or encouraged by EPA, other kinds of studies involving human subjects intentionally exposed to pesticides have occasionally been submitted to the Agency voluntarily. Among these voluntarily submitted studies there have been tests involving intentional dosing of human subjects to establish a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity of certain pesticides to humans. For some two decades before passage of the Food Quality Protection Act (FQPA) in 1996, submission of such studies was rare. EPA considered and relied on human NOAEL/NOEL studies in a few regulatory decisions on pesticides made

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<sup>1</sup> See 45 CFR Subpart B for women, fetuses, and certain neonates, Subpart C for prisoners, and Subpart D for children.

prior to 1996. After passage of FQPA, submission of these types of studies to the Office of Pesticide Programs increased; the Agency has received some twenty studies of this kind since 1996.

Human study research done by third parties may be governed by specific institutional policies intended to protect research subjects, may fall within the scope of the Declaration of Helsinki, or might actually be covered by the Common Rule if the particular testing institution has a Federal wide Assurance that includes such a requirement. In some instances, research is reported in a such a manner that EPA cannot readily determine whether institutional policies are consistent with or as protective of human subjects as the Common Rule, or even the extent to which such policies or standards have been followed in the conduct of any particular study. Thus, even well-conducted third-party human studies may raise difficult questions for the Agency when it seeks to determine their acceptability for consideration.

Therefore, the Agency through this Notice is proposing to require third parties who conduct certain kinds of human research to comply with the Common Rule. In addition, EPA is also proposing to adopt the protections contained in HHS' subpart B regulations (additional protection for pregnant women and subpart D regulations (additional protection for children).

## **2.1 Need for Federal Regulation**

The need for a federal regulation to extend the Common Rule to third-party human studies stems from the existence of conditions that are described in economic theory as “market failure” resulting from “asymmetric information.” Economic theory suggests that regulatory intervention is justified in the presence of such market failure.

For human research, the “asymmetric information” problem arises if the human subjects do not have as much information as the researchers about the level of risk they could face when participating in the human subject studies. Without such information, they cannot make a fully informed choice about whether to volunteer for the research. Regulatory intervention would be necessary to protect human subjects by ensuring that the researchers will follow appropriate standards regarding informed consent.

The proposed rule will provide more protection to human subjects, to enhance the efficiency of submitting human studies to EPA by third parties and reviewing the ethical aspects of the studies by EPA in the regulatory rule-making process.

## **2.2 Authority for the Human Studies Rule**

The proposed rulemaking is authorized under a variety of provisions of the different environmental statutes EPA administers. Section 25(a) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) gives the Administrator authority to “prescribe regulations to carry out the purposes of [FIFRA].” Such a rule would further implement EPA’s authority to require data

in support of registration of pesticides (see, for example, FIFRA sections 3(c)(1)(F) and 3(c)(2)(B)) and to interpret the provision making it unlawful for any person “to use any pesticide in tests on human beings unless such human beings are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable, and (ii) freely volunteer to participate in the test.” (FIFRA sec. 12(a)(2)(P)). In addition, section 408(e)(1)(C) of the Federal Food, Drug and Cosmetic Act (FFDCA) authorizes the Administrator to issue a regulation establishing “general procedures and requirements to implement this section.”

In addition, EPA has broad authority under 5 U.S.C. 301 (governing agency regulations) and 42 U.S.C. 300v-1(b) (authorizing the Commission that developed the Common Rule). The latter two statutory provisions constitute the legal basis cited for the Common Rule when it was promulgated in 1991.

### **2.3 Agency Proposed Changes to the Common Rule**

This section briefly summarizes the proposed changes to the Common Rule that would strengthen the protections for individuals who participate as human subjects in covered human research conducted by EPA, conducted by entities with support from EPA, or conducted by third parties with the intent of submitting data and/or information resulting from such research to EPA under FIFRA or FFDCA

EPA proposes:

- 1) Extending the requirements of the Common Rule (40 CFR Part 26.101 – 26.124) prospectively to third-party research involving intentional exposure of human subjects, if the researcher intended to submit the resulting information to EPA, or to hold the information for later inspection by EPA, under FIFRA or FFDCA.
- 2) Requiring prior submission of protocols and related information for proposed human research covered by the rule. This rule as proposed would apply to the same range of research to which the Common Rule would be extended-i.e. all intentional dosing human studies intended for submission to EPA under the pesticide laws. EPA also proposes to establish a Human Studies Review Board to provide an additional scientific and ethical peer review for such research. Finally, the Agency proposes to require that submitted reports of covered third-party studies include detailed information about the ethical conduct of the studies. The proposal also specifies the range of information to be provided with submitted protocols, and with the results of the research. This list of topics is derived from the Common Rule criteria for IRB approval of proposed research at 40 CFR 26.111. This information will have been gathered for presentation to the IRB, and it should not be any additional burden to provide the same range of information to the Agency. Any third party who intends to conduct human research covered by the Common Rule, as specified in proposed section 26.101(j), shall, after receiving

approval from all appropriate Institutional Review Boards (IRBs), submit to EPA at least 90 days prior to initiating such research all information relevant to the proposed research specified by section 26.115(a) to be prepared and maintained by an IRB, and the following additional information, to the extent not otherwise covered:

- (a) a discussion of:
  - (i) the potential risks to human subjects;
  - (ii) the measures proposed to minimize risks to the human subjects;
  - (iii) the expected benefits of such research, and to whom they would accrue;
  - (iv) alternative means of obtaining information comparable to what would be collected through the proposed research; and
  - (v) the distribution and balance of risks and benefits of the proposed research;
- (b) the information for subjects and written informed consent agreements as provided to the IRB, and as approved by the IRB;
- (c) information about how subjects will be recruited, including any advertisements proposed to be used; and
- (d) all correspondence between the IRB and either the investigators or sponsors.

Any person who submits to EPA data derived from human research covered by this subpart shall also provide to EPA information documenting compliance with the requirements of this subpart. Such information should include:

- (a) copies of all of the records relevant to the research specified by section 26.115(a) to be prepared and maintained by an IRB;
  - (b) copies of records documenting informed consent as specified by section 26.117, but not identifying any subjects of the research; and
  - (c) copies of all correspondence, if any, between EPA and the researcher or sponsor pursuant to section 26.124(b).
- 3) Categorically prohibiting third parties engaged in research covered by the proposed extension of the Common Rule from conducting any study involving intentional dosing of children, and to apply the same prohibition to human research that EPA conducts or supports. EPA further proposes to prohibit its own reliance on any research involving intentional dosing of children with pesticides. Finally, as recommended by the National Academy of Sciences (NAS), EPA proposes to adopt formally additional protections for children as subjects of research which it has long applied in research which it conducts or supports.

- 4) Categorically prohibiting third parties engaged in research covered by the proposed extension of the Common Rule from conducting any study involving intentional dosing of pregnant women, fetuses, or newborns, and to apply the same prohibition to human research that EPA conducts or supports. EPA further proposes to prohibit itself from relying in its decision-making on research involving intentional dosing of pregnant women, fetuses, or newborns. Finally EPA proposes to adopt formally additional protections for pregnant women, fetuses, and newborns as subjects of research which it has long applied in research it conducts or supports.
- 5) Discouraging the submission under FIFRA or FFDCA of ethically deficient third-party human subjects research, EPA proposes, as circumstances warrant, to (1) refuse to rely on the results of any research that does not comply with the requirements of FIFRA section 12(a)(2)(P); (2) seek withdrawal of a research institution's federal-wide assurance; (3) disqualify a research institution or its IRB; (4) debar an entity from receiving federal funds for research; or (5) present for public review an objective analysis of the ethical deficiencies of any human research relied upon by EPA for regulatory decision-making under any statutory authority. These provisions in proposed sections 26.501 - 26.504 and 26.506 closely follow FDA's existing regulations in 21 CFR section. 56.120 - 56.124.
- 6) In a new Subpart F, ethical standards for its decisions to rely on or not to rely on in its decision-making reports of completed intentional- dosing research with human subjects being considered under FIFRA or FFDCA. For covered types of research conducted after the effective date of the rule, EPA proposes to refuse to rely on data from scientifically sound and relevant human research unless EPA has adequate information demonstrating that the research complied with the Common Rule. For covered types of research conducted before the effective date of the rule, EPA proposes to rely on data from scientifically sound and relevant human research unless there is clear evidence to show the conduct of the research was fundamentally unethical or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. EPA also proposes a formal process to make an exception to these standards when reliance on scientifically sound but ethically deficient research would give crucial support to a regulatory action more protective of public health than could be justified without relying on the ethically deficient research.

## **2.4 Profile of the Affected Entities**

For entities regulated under FIFRA, the proposed rule would affect pesticide registrants. The market structure of the basic pesticide producing industry can be described as a moderately to highly concentrated oligopoly, with only about 20 basic producers of common U.S. pesticides. Relatively few firms produce the bulk of products, and a few particular products tend to dominate national, regional, and local markets for individual site/pest combinations. Individual firms tend to significantly influence supply and prices in the markets in which they compete. A

detailed profile for the conventional pesticide industry, including information on product classes for firms registering conventional pesticides is presented in Appendix D.

### **3 Options Considered for the Proposed Human Studies Rule**

For estimating the potential impact of the proposed rule, the costs and benefits were analyzed for the four options and compared with those for the baseline that represents the current practice. Under the current practice, third parties are currently complying with the Common Rule when submitting to the Agency intentional exposure studies and the Agency currently reviews information pertaining to the ethical conduct. The economic analysis focuses on the cost and benefits to industry and the Agency associated with human studies performed after the publication of the rule.

The baseline is defined in EPA's guidelines for preparing economic analyses (12) as what the world is likely to be in the future in the absence of the proposed rule. In the absence of the proposed rule, the current practice of reviewing third-party intentional exposure studies on a case-by-case basis will continue. Therefore, the baseline in this analysis is assumed to be the current practice.

The incremental benefits and costs are the differences in the benefits and costs between the current practice and the proposed rule. However, the current practice is different from the regulatory baseline (40 CFR Part 26) under which third parties are not required to comply with the Common Rule and there would be no compliance costs to third parties and the Agency. If the regulatory baseline is instead used to estimate the incremental benefits and costs of the proposed rule, the estimates would be greater than those calculated in this analysis by \$159K - \$196K for industry and \$113K for the Agency (see Appendix C for more details).

#### **Option 1**

This option is no change to the current practice, which is the baseline in this analysis. The Agency currently reviews information pertaining to the ethical conduct of completed third-party intentional exposure studies to identify or quantify toxic effect under the authority of FIFRA or FFDCA, and other intentional exposure studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide.

Intentional exposure studies conducted by third parties are not currently required to meet the Common Rule; however, most, if not all, are currently complying with the Common Rule including subparts B and D for intentional exposure studies or following other largely equivalent international guidelines such as the Declaration of Helsinki.

For human studies not involving intentional dosing exposure, the Agency is not currently requiring third parties to submit information pertaining to the ethical conduct of completed human studies. Third parties are not required to comply with the Common Rule for such human studies, although many are generally responsive to the EPA's guideline requirements which often refer to the Common Rule.

## **Option 2**

This option is to extend the requirements of the Common Rule only to third-party studies involving intentional human exposure to identify or quantify toxic effects, and intended for submission to EPA under the authority of FIFRA or FFDCA and to prohibit third parties (and EPA) from conducting such studies with pregnant women or children. Under this option, researchers intending to conduct such human studies are also required to submit protocols for EPA's review prior to initiating the research. In addition, the Human Studies Review Board (HSRB) will conduct secondary review of protocols and completed human studies once they are reviewed by EPA staff. This is not part of the current practice.

## **Option 3**

This option, which reflects the rule being proposed by EPA, is to extend the requirements of the Common Rule to all intentional dosing studies intended for submission to EPA under the authority of FIFRA or FFDCA and to prohibit third parties (and EPA) from conducting such studies with pregnant women or children. Under this option, researchers intending to conduct such human studies are also required to submit protocols for EPA's review prior to initiating the research. In addition, the Human Studies Review Board (HSRB) will conduct secondary review of protocols and completed human studies once they are reviewed by EPA staff.

## **Option 4**

This option is to extend the requirements of the Common to all third-party studies intended for submission to EPA under the authority of FIFRA or FFDCA and to prohibit third parties (and EPA) from conducting such studies with pregnant women or children. Under this option, researchers intending to conduct such human studies are also required to submit protocols for EPA's review prior to initiating the research. In addition, the Human Studies Review Board (HSRB) will conduct secondary review of protocols and completed human studies once they are reviewed by EPA staff.

## **4. Benefits of the Proposed Human Studies Rule**

The proposed rule will benefit human subjects, third party researchers (industry), the public, the Agency, and others who are affected by the proposed rule. This section qualitatively describes potential benefits of the proposed rule to the affected entities under the four options.

### **Option 1**

Option 1 is no change to the current practice of reviewing the ethical aspects of third-party intentional dosing studies on a case-by-case basis. There will be no incremental benefit to the affected entities under this option.

### **Option 2**

There are limited direct benefits of the proposed rule to human study participants including vulnerable populations. Since most, if not all, researchers conducting intentional exposure studies are currently following the Common Rule, EPA expects only a small percentage of future human studies (and the volunteers in those studies) to be affected. The

benefits may, however, be somewhat greater if the final rule covers human research beyond intentional exposure studies.

Those who voluntarily sponsor third-party human research intended for submission to EPA can be assumed to believe it will be to their advantage to do so. A well-designed and conducted human study could support the elimination of certain default assumptions used to estimate human responses from animal data, and thus potentially lead to a less restrictive regulatory posture toward the substance tested. For example, the economic motivation for companies to conduct human subject studies on pesticides is asserted to be to justify reducing a 10-fold interspecies uncertainty factor used to calculate reference doses, thereby reducing the calculated risk from exposure to pesticides. Such a decrease in calculated risk might allow the company to sell more of their pesticides in the market. It should be noted, however, that the results of such studies could also lead to an increase in calculated risks and therefore provide a basis for potentially more restrictive regulatory requirements that would lead to greater protection of public health. Because it is not possible to predict the impact of future studies on EPA risk assessments and regulatory actions, EPA did not attempt to include any such potential impacts in its assessment of the benefits of this rule-making.

The proposed rule would require any third parties conducting covered research to obtain adequate independent scientific and ethical review to ensure protection of the study participants. Thus, the potential benefits of the proposed rule to third parties will derive from their better understanding of what standards would be applied in the future during the Agency's review process, which will then lead to a more efficient process in preparing submissions to EPA. It will reduce uncertainty associated with the regulatory process and reduce the costs associated with positioning existing and potential uses in the regulatory process and in the market.

The main benefits of the proposed rule to the Agency are through clarification of the standards to be applied to third-party human research considered by the Agency, which might result in savings in costs associated with case-specific decision-making. The Agency currently reviews human subject studies submitted to EPA on a case-by-case without established standards and criteria. By establishing rules to guide this practice, the Agency will add more efficiency in reviewing the human subject studies in regulatory decision-making process.

Other potential benefits associated with human subject studies are societal. The proposed rule extending the Common Rule to certain research by third parties will provide some assurance for the public that newly conducted third-party human studies considered by EPA in its regulatory decision-making will be scientifically sound and ethically acceptable, which should result in greater public confidence in and acceptance of Agency decisions.

In addition, this option will provide a further increment of protection for the human subjects of future studies that would not otherwise have been mandated by the Common Rule. The Agency's review of the study protocols prior to human studies are initiated will provide an added layer of protection to human subjects. For the third parties, it will also increase the likelihood that the studies are scientifically sound and ethically acceptable under EPA's standards when they are completed. As such, the proposed rule will reduce the uncertainty third

parties may experience when submitting human studies without a clear, transparent process for evaluating whether the studies meet ethical and scientific standards for human studies. The increased certainty resulting from this rule will reduce the costs of re-work. Moreover, it will reduce the opportunity cost of waiting for Agency process to take place before knowing whether to establish additional investments in supporting the chemical through the regulatory process.

The Agency's ability to make sound regulatory decisions will be enhanced. EPA's awareness of all on-going human subject studies would help ensure that such studies would be included in the EPA regulatory or risk-assessment process. After the studies are completed and submitted to EPA, the Agency would have a better understanding of whether, and to what extent, the results of the studies should be considered. It will also provide additional assurance for the public that the third-party human studies are conducted in such a way to meet high scientific and ethical standards and used as input to the regulatory decision-making process.

### **Option 3**

As explained under Option 2, this option will benefit the affected entities including human subjects, third parties, the Agency, and the public. Since options 2 and 3 involve the same substantive standards, the benefits under both options will be qualitatively the same. However, Option 3 is not confined only to third-party intentional exposures studies to identify or quantify toxic effects, and intended for submission to EPA under the authority of FIFRA or FFDCA. Since this category of human research is greater than the research described for option 2, the benefits of option 3 will be quantitatively greater than for option 2.

### **Option 4**

Like Option 2 and 3, this option will benefit the affected entities including human subjects, third parties, the Agency, and the public. Option 4 is not confined only to third-party intentional exposures studies intended for submission to EPA under the authority of FIFRA or FFDCA. The benefits of Option 4 will be quantitatively greater than for Option 2 and 3.

## **5 Costs of the Proposed Human Studies Rule**

This section briefly describes the costs of the proposed human studies rule and of other options evaluated. The impact of the proposed rule on the regulated community is primarily defined as the incremental cost to third parties submitting human studies to EPA of complying with the Common Rule. The cost of the proposed rule to the Agency is the cost of reviewing the ethical and scientific aspects of proposed human research protocols and the ethics of completed human studies.

### **5.1 Methodology for the Cost Analysis**

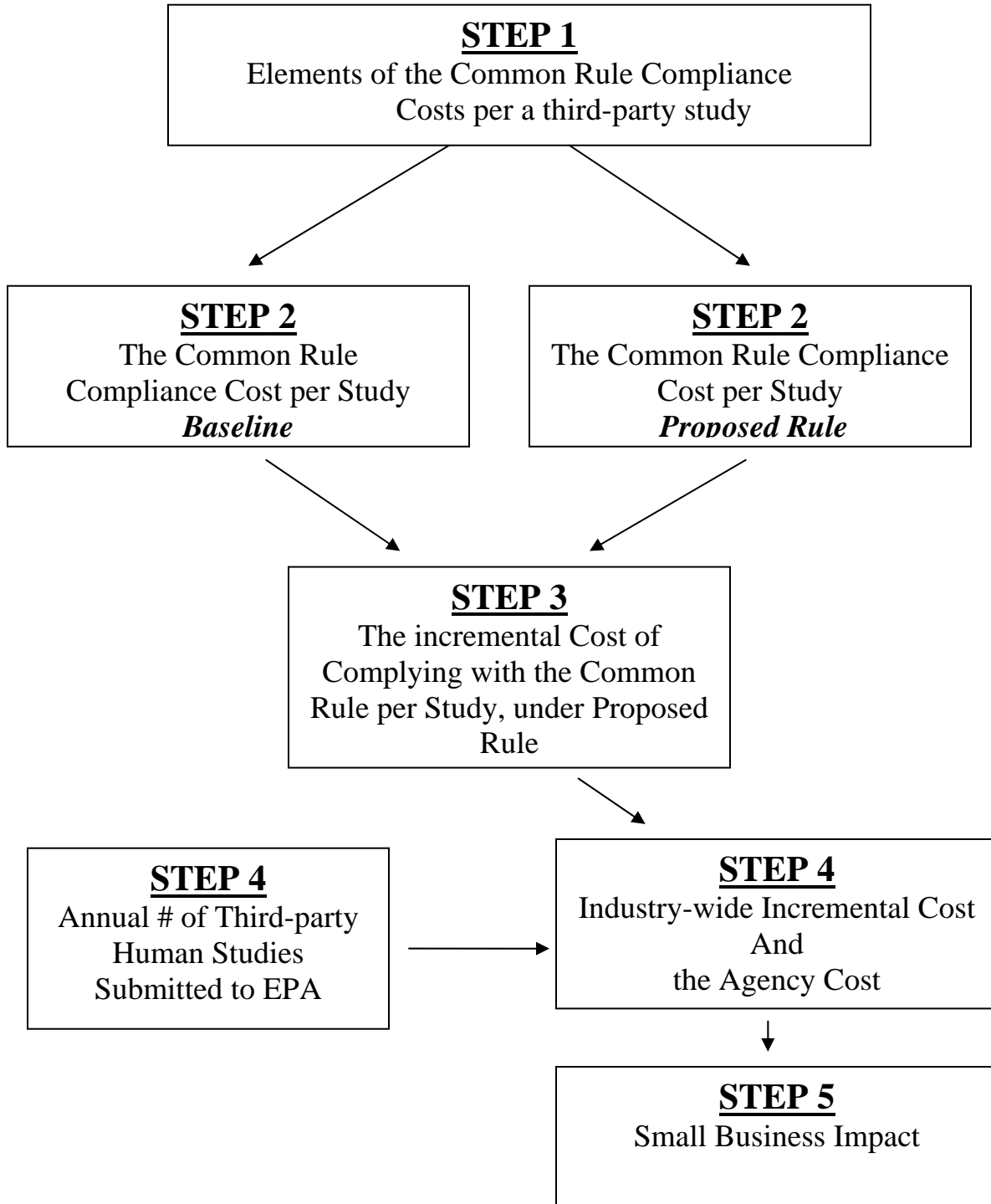
This section describes the method and data used to quantitatively assess the costs of complying with the proposed rule to industry and the Agency. The compliance costs were estimated for the four options that the Agency is proposing. The estimated costs of the four options were compared with the estimated cost of the baseline that represents the current

practice. The incremental costs to industry and the Agency were calculated in the following 5 steps:

- Step 1. Determine the *elements* of the Common Rule compliance costs per study to a third party and to the Agency
- Step 2. Determine the *compliance costs per study* to a third party and to the Agency under the baseline and the proposed rule
- Step 3. Determine the *incremental costs per study* to a third party and to the Agency
- Step 4. Determine the total incremental costs to industry and to the Agency, through *the number of studies submitted per year*
- Step 5. Small Business Impact

Chart 5-1 is a flow chart describing the methodology. The elements of the compliance costs per study (Step 1) are estimated and then aggregated to calculate the compliance costs per study to a third party and to the Agency under the baseline and the proposed rule (Step 2). The incremental costs per study (Step 3) to a third party and to the Agency are estimated by comparing the compliance costs under the baseline with the compliance costs under the proposed rule. The annual costs to industry and to the Agency (Step 4) are then determined by multiplying the incremental costs per study by the estimated number of human studies for the baseline and the proposed rule. Finally, small business impacts were briefly discussed (Step 5).

**Chart 5-1: Methodology Flowchart**



### 5.1.1 Industry Costs

The annual cost to industry to comply with the Common Rule can be described as:

$$1) \text{ Cost}_{\text{industry}} = \sum_{i=1}^n \text{Cost}_{\text{third-party}} = \sum_{i=1}^n (\text{IRBC}_i + \text{IRC}_i + \text{IPC}_i)$$

where,

<b>Cost<sub>industry</sub></b> :	Industry cost (all third parties submitting human studies) per year
<b>Cost<sub>third-party</sub></b> :	Cost to a third party i, where i = 1, ..., n, the number of human studies submitted annually to EPA
<b>IRBC<sub>i</sub></b> :	Institutional Review Board (IRB) <sup>2</sup> review cost per study to a third-party.
<b>IRC<sub>i</sub></b> :	Cost to a third-party i for preparing and submitting information pertaining to the ethical conduct of a completed human study to EPA
<b>IPC<sub>i</sub></b> :	Cost to a third-party i for preparing and submitting a protocol to EPA for science and ethics review

The cost to a third party (**Cost<sub>third-party</sub>**) is the sum of the IRB review cost (**IRBC**); the cost for preparing and submitting information pertaining to the ethical conduct of a completed human study to EPA (**IRC**); and the cost for submitting a protocol to EPA for science and ethics review before the study is initiated (**IPC**). The industry cost (**Cost<sub>industry</sub>**) is estimated by multiplying **Cost<sub>third-party</sub>** by **N**, the number of human studies submitted to EPA per year. The incremental cost to industry is then estimated by comparing **Cost<sub>industry</sub>** under the baseline with **Cost<sub>industry</sub>** under the each option of the proposed rule.

The estimated industry costs would be different among the four options considered. Under Option 1, there is no change from current practice which is the baseline in this analysis. Therefore no additional cost is incurred under this option. Third parties are currently complying with the Common Rule for human studies involving intentional dosing exposure and as a result, they currently incur **IRBC** and **IRC**. For studies not involving intentional dosing exposure, it is assumed that third parties are currently not complying with the Common Rule (**IRBC =0 and IRC=0**).

Under Option 2, third parties would be required to comply with the Common Rule only for intentional exposure studies to identify or quantify toxic effects, and intended for submission to EPA under the authority of FIFRA or FFDCFA. Third parties are also required to submit their

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<sup>2</sup> An IRB is a committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. Human clinical trials conducted or supported by the federal government must be approved by an IRB before they begin. Every institution that conducts or supports such research must, by federal regulation, have an IRB that initially approves and periodically reviews the research so as to protect the rights of human subjects.

protocols for EPA's review prior to initiating the research. Under this option, because they are currently in compliance with the Common Rule, the additional cost to industry would be **IPC** for the 14 intentional dosing studies to identify or quantify toxic effects, and intended for submission to EPA under FIFRA or FFDCA.

Under Option 3, third parties would be required to comply with the Common Rule for all intentional exposure studies intended for submission to EPA under the authority of FIFRA or FFDCA. Third parties are also required to submit their protocols for EPA's review prior to initiating the research. Under this option, additional cost to industry would be **IPC** for the 30 intentional dosing studies.

Under Option 4, third parties are required to comply with the Common Rule for all human studies and are also required to submit their protocols for EPA's review prior to initiating the research. Under this option, additional cost to industry would be **IRBC** and **IRC** for 32 studies not involving intentional human exposure and **IPC** for all 62 human studies.

IRB review cost per study to a third-party (**IRBC**) ranges from \$4,565 to \$5,818 per study. The cost to industry was estimated at a range due to this range estimate of **IRBC**. It was estimated from the five academic and commercial IRB fee schedules (1, 2, 3, 4, and 5). Appendix A details the five IRB fee schedules used in this analysis. We assumed the duration of a typical human study is 5 years<sup>3</sup>. The study duration affects the **IRBC** because continuing review is generally recurring annually. The breakdown of IRB costs are:

- 1) Initial review (\$1,250 – \$2,000);
- 2) 4 continuing reviews (\$2,000 - \$3,360);
- 3) 1 modification (\$200 - \$525); and
- 4) Investigator expenses for preparing protocol for IRB review (\$415 - \$528)

The **IRBC** estimate in this analysis is close to the estimate used by the Federal Food and Drug Administration (FDA). In assessing annualized cost burden to industry, FDA estimated \$5,000 (\$50 times 100 hours) per study for an IRB review (8).

The cost to a third-party for preparing and submitting information pertaining to the ethical conduct of a completed human study to EPA (**IRC**) was estimated to be \$727. Cost to a third-party for preparing and submitting a protocol to EPA for science and ethics review (**IPC**) was estimated to be \$538. Table 5-1 and 5-2 detail the calculation of **IRC** and **IPC**, respectively. The cost estimates for **IRC** and **IPC** are, however, uncertain because they were derived from the Agency assumptions on burden hours and wages for each activity that include rule familiarization and training; preparing and submitting information; and storing, filing, and maintaining information.

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<sup>3</sup> The typical study period for the clinical studies on pesticide use and exposure is 5 years from the database maintained by the U.S. National Institute of Health (9).

**Table 5-1: Calculation of IRC per Human Study**

Burden Hours (per year)					
Activity Items for IRC	Managerial (\$96)*	Technical (\$63)*	Clerical (\$32)*	Total Hour	Cost \$
Rule familiarization and training	1	1	0	2	\$159
Prepare and submit ethics information of completed human studies to EPA	0	8	1	9	\$536
Store, file and maintain information	0	0	1	1	\$32
<b>Total</b>	<b>1</b>	<b>9</b>	<b>2</b>	<b>12</b>	<b>\$727</b>

\*Wage rates were from US EPA (2005). "Methodology to Estimate the Personal Wages Associated with the Reporting of Information Collection Request (11)."

**Table 5-2: Calculation of IPC per Human Study**

Burden Hours (per year)					
Activity Items for IPC	Managerial (\$96)*	Technical (\$63)*	Clerical (\$32)*	Total Hours	Cost \$
Rule familiarization and training	1	1	0	2	\$159
Prepare and Submit a protocol to EPA	0	5	1	6	\$347
Store, file and maintain information	0	0	1	1	\$32
<b>Total</b>	<b>1</b>	<b>6</b>	<b>2</b>	<b>9</b>	<b>\$538</b>

\*Wage rates were from US EPA (2005). "Methodology to Estimate the Personal Wages Associated with the Reporting of Information Collection Request (11)."

The annual average number of all human studies submitted to the Office of Pesticide Program (OPP) at EPA is estimated to be 62. Appendix B summarizes the record of human studies submitted to OPP from 1996 to 2001. On average, 30 studies involving intentional dosing exposure and 32 studies not involving intentional dosing exposure were submitted to OPP annually from 1996 to 2001. Among the 30 intentional exposure studies, fourteen studies are projected to be intentional exposure studies to identify or quantify toxic effects, and intended for submission to EPA under the authority of FIFRA or FFDCA. Such intentional exposure studies involve skin tests (for irritancy, sensitization, or photo response), or systemic toxicity. Table 5-3 below summarizes the incremental cost for industry under the four options.

**Table 5-3: Industry Incremental Cost under the Four Options**

		IRBC	IRC	IPC	N*	Incremental Cost N×(IRBC+IRC+IPC)
Option 1 (Current Practice)	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$0	\$0	\$0	14	\$0
	Other intentional exposure studies	\$0	\$0	\$0	16	\$0
	Studies not involving intentional dosing exposure	\$0	\$0	\$0	32	\$0
	<b>Total Industry Incremental Cost for Option 1: \$0</b>					
Option 2	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$0	\$0	\$538	14	\$7,532
	Other intentional exposure studies	\$0	\$0	\$0	16	\$0
	Studies not involving intentional dosing exposure	\$0	\$0	\$0	32	\$0
	<b>Total Industry Incremental Cost for Option 2: \$7,532</b>					
Option 3	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$0	\$0	\$538	14	\$7,532
	Other intentional exposure studies	\$0	\$0	\$538	16	\$8,608
	Studies not involving intentional dosing exposure	\$0	\$0	\$0	32	\$0
	<b>Total Industry Incremental Cost for Option 3: \$16,140</b>					
Option 4	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$0	\$0	\$538	14	\$7,532
	Other intentional exposure studies	\$0	\$0	\$538	16	\$8,608
	Studies not involving intentional dosing exposure	\$4,565 - \$5,818	\$727	\$538	32	\$186,560 - \$226,656
	<b>Total Industry Incremental Cost for Option 4: \$202,700 - \$242,796</b>					

\*Number of human studies annually submitted to EPA

### 5.1.2 Agency Costs

The Agency costs of complying with the proposed rule can be described as:

$$2) \quad ACost_{EPA} = \sum_{i=1}^n ACost_i = \sum_{i=1}^n (ARC_i + APC_i) + HSRBC$$

where,

<b>ACost<sub>EPA</sub></b> :	Total cost to the Agency for reviewing protocols and ethics information of completed human studies plus the costs of reviewing protocols and completed human studies by Human Studies Review Board (HSRB)
<b>ACost<sub>i</sub></b> :	Cost to the Agency (Office of Pesticides Programs (OPP)) for the primary review of a protocol and ethics information of a completed human studies submitted by a third party i, where i = 1, ..., N.
<b>ARC<sub>i</sub></b> :	Agency cost for reviewing, processing, and filing ethics information of a completed human studies submitted by a third party i.
<b>APC<sub>i</sub></b> :	Agency cost for reviewing, processing, and filing a protocol for science and ethics review submitted by a third party i.
<b>HSRBC</b> :	Cost to the Agency for the secondary review of protocols and completed human studies by HSRB.

The cost to the Agency per study (**ACost**) is the sum of agency cost for reviewing, processing, and filing ethics information of a completed human study (**ARC**) and a protocol for science and ethics review (**APC**) submitted by a third party, plus the cost to the Agency per study for the secondary review of protocols and completed human studies by HSRB (**HSRBC**). The total cost to the Agency (**ACost<sub>EPA</sub>**) is estimated by multiplying **ACost** by N, the number of human studies submitted to EPA. The incremental cost to the Agency is then estimated by comparing **ACost<sub>EPA</sub>** under the baseline with **ACost<sub>EPA</sub>** under the each option of the proposed rule.

The estimated agency costs are different among the four options. Under Option 1, the Agency currently incurs **ARC** and will begin to incur **APC** if third parties submit proposed protocols for EPA review, and therefore no incremental cost will be incurred to the Agency under this option.

Under Options 2, additional cost to the Agency would be **APC** and **HSRBC** for the 14 intentional exposure studies to identify or quantify toxic effects, and intended for submission to EPA under the authority of FIFRA or FFDCA. Under Options 3, additional cost to the Agency would be **APC** and **HSRBC** for the 30 all intentional exposure studies. Under Option 4, the

Agency incurs **ARC, APC, and HSRBC** for 32 studies not involving intentional human exposure and incurs **APC and HSRBC** for 30 intentional dosing studies.

The cost to the Agency for reviewing, processing, and filing ethics information of a completed human study (**ARC**) is estimated to be \$2,091 when third parties are required to submit protocols to EPA. **ARC** is estimated to be \$3,751 when third parties are not required to submit protocols to EPA. This is because the Agency’s prior review on the protocols would reduce the hour burden for reviewing ethics information of completed human studies later. **APC** is estimated to be \$4,581.

Table 5-4 and 5-5 detail the calculation of **ARC** and **APC**, respectively. The cost estimates for **ARC** and **APC** are, however, uncertain because they were derived from the Agency assumptions on burden hours and wages for each activity that include rule familiarization and training; reviewing a protocol and/or a completed study; recording and reporting information; and storing, filing, and maintaining information.

Under the proposed rule, the Human Studies Review Board (HSRB) will conduct secondary review of protocols and completed human studies once they are reviewed by EPA staff. The HSRB members are independent experts in the areas of science and ethics. This is not part of the current practice. In this analysis, we assume that each independent HSRB members are paid \$600 per day. It is assumed that the HSRB meets 10 times a year and has 10 members. It is also assumed that each meeting for Option 2 takes 3 days, 4 days for Option 3, and 5 days for Option 4. As a result, **HSRBC** was estimated to be \$180,000 for Option 2, \$240,000 for Option 3, and \$300,000 for Option 4. Table 5-6 below summarizes the cost estimates for calculating the Agency costs under the four options.

**Table 5-4: Calculation of ARC per Human Study**

Activity Items for ARC	Burden Hours (per year)				Cost \$
	Managerial (\$115)*	Technical (\$83)*	Clerical (\$59)*	Total Hours	
Rule familiarization and training	1	1	0	2	\$198
Review the ethics of a completed human study	1	20 (40)**	0	21	\$1,775 (\$3,435)**
Record and report information	0	0	1	1	\$59
Store, file and maintain information	0	0	1	1	\$59
<b>Total</b>	<b>2</b>	<b>21</b>	<b>2</b>	<b>25</b>	<b>\$2,091</b> <b>(3,751)**</b>

\*Wage rates were from US EPA (2005). “Methodology to Estimate the Personal Wages Associated with the Reporting of Information Collection Request (11).”

\*\*Numbers in parenthesis are for the case when the Agency does not review protocols prior to initiating the research.

**Table 5-5: Calculation of APC per Human Study**

Activity Items for APC	Burden Hours (per year)				Cost \$
	Managerial (\$115)*	Technical (\$83)*	Clerical (\$59)*	Total Hours	
Rule familiarization and training	1	1	0	2	\$198
Review scientific and ethical aspect of a protocol	1	50	0	51	\$4,265
Record and report information	0	0	1	1	\$59
Store, file and maintain information	0	0	1	1	\$59
<b>Total</b>	<b>2</b>	<b>51</b>	<b>2</b>	<b>55</b>	<b>\$4,581</b>

\*Wage rates were from US EPA (2005). "Methodology to Estimate the Personal Wages Associated with the Reporting of Information Collection Request (11)."

**Table 5-6: Agency Incremental Cost under the Four Options**

		ARC	APC	N*	Incremental Cost [N×(ARC+APC)]
Option 1 (Current Practice)	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$0	\$0	14	\$0
	Other intentional exposure studies	\$0	\$0	16	\$0
	Studies not involving intentional dosing exposure	\$0	\$0	32	\$0
	<b>HSRBC for Option 1 : \$0</b>				
<b>Total Agency Incremental Cost for Option 1: \$0</b>					
Option 2	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$-1,660**	\$4,581	14	\$40,894
	Other intentional exposure studies	\$0	\$0	16	\$0
	Studies not involving intentional dosing exposure	\$0	\$0	32	\$0
	<b>HSRBC for Option 2: \$180,000</b>				
<b>Total Agency Incremental Cost for Option 2: \$220,894</b>					
Option 3	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$-1,660**	\$4,581	14	\$40,894
	Other intentional exposure studies	\$-1,660**	\$4,581	16	\$46,736
	Studies not involving intentional dosing exposure	\$0	\$0	32	\$0
	<b>HSRBC for Option 3: \$240,000</b>				
<b>Total Agency Incremental Cost for Option 3: \$327,630</b>					
Option 4	Studies involving intentional dosing exposure to identify or quantify toxic effects	\$-1,660**	\$4,581	14	\$40,894
	Other intentional exposure studies	\$-1,660**	\$4,581	16	\$46,736
	Studies not involving intentional dosing exposure	\$2,091	\$4,581	32	\$213,504
	<b>HSRBC for Option 4: \$300,000</b>				
<b>Total Agency Incremental Cost for Option 4: \$601,134</b>					

\*Number of human studies annually submitted to EPA

\*\*\$-1,660 is \$2,091 less \$3,751. The Agency’s prior review on the protocols would reduce **ARC** by \$1,660 per review.

## 5.2 Results for the Cost Analysis

Table 5-7 summarizes the costs to industry and the Agency under the four options, and their incremental costs from the baseline which is the current practice. Appendix C details the estimation of the incremental costs to industry and the Agency under the four options.

**Table 5-7: Incremental Costs to Industry and the Agency under the Four Options**

	<b>Baseline (Current Practice)</b>	<b>Option 1</b>	<b>Option 2</b>	<b>Option 3</b>	<b>Option 4</b>
Cost to Industry	\$158,760 - \$196,350	\$158,760 - \$196,350	\$166,292 - \$203,882	\$174,900 - \$212,490	\$361,460 - \$439,146
Incremental Cost to Industry		\$0	\$7,532	\$16,140	\$202,700 - \$242,796
Cost to the Agency	\$112,530	\$112,530	\$333,424	\$440,160	\$713,664
Incremental Cost to the Agency		\$0	\$220,894	\$327,630	\$601,134

### **Option 1**

Option 1 is no change to the current practice. There will be no incremental cost of the proposed rule to industry and the Agency. Industry (third parties) currently incurs \$159K to \$196K annually associated with the current practice of complying with the Common Rule for human studies involving intentional human exposure. The Agency currently incurs \$113K annually for reviewing the ethical aspects of such studies on a case-by-case basis.

### **Option 2**

Under this option, the incremental costs to industry were estimated to be \$8K for preparing and submitting protocols for EPA's review prior to initiating the research for 14 human studies involving intentional human exposure to identify or quantify toxic effects, and intended for submission to EPA under FIFRA or FFDCa. The incremental costs to the Agency were estimated to be \$221K for reviewing, processing, and filing protocols by EPA staff and the secondary review of protocols and completed human studies by HSRB for such intentional dosing studies.

### **Option 3**

Under this option, the incremental cost to industry were estimated to be \$16K for preparing and submitting protocols for EPA's review prior to initiating the research for 30 human studies involving intentional human exposure. The Agency will incur \$328K for reviewing, processing,

and filing protocols by EPA staff and the secondary review of protocols and completed human studies by HSRB.

#### **Option 4**

Under this option, the incremental costs to industry were estimated to be \$203K to \$243K, and \$601K to the Agency. This cost to industry was estimated as a range due to **IRBC** that ranges from \$4,565 to \$5,818 per study. The incremental costs to industry and the Agency are mainly attributable to the studies not involving intentional dosing exposure that will need to comply with the Common Rule under this option.

## **6. Small Business Impact**

This section describes the method for defining and identifying the small entities affected by the rule. The impacts on small entities of complying with the Proposed Human Protection rule compared to their annual sales revenue.

### **6.1 Regulatory Overview**

The Regulatory Flexibility Act (RFA) of 1980 and its 1996 amendment, the Small Business Regulatory Enforcement Fairness Act (SBREFA) require that special consideration be given to the effects of proposed regulations on small business entities. The regulations require that a determination be made as to whether the proposed regulation will have a significant impact on a substantial number of small entities. EPA measured the economic impact by the annual compliance costs as a percentage of sales to assess the small business impacts.

### **6.2 Categorization of Small Businesses**

The Small Business Act authorizes the Small Business Administration (SBA) to establish the definition of a small business. The SBA has set size standards under the North American Industrial Classification System (NAICS), using various thresholds on employee number and revenue amount, which vary by NAICS code. In determining the size of a firm, the SBA applies its standards to the parent level of a business entity.<sup>4</sup> The SBA also bases its determinations on the primary industry of the firm. In this analysis, the firm's primary NAICS code is assumed to be its primary industry, and the definition of small business is determined by the SBA based on maximum number of employees or sales for small businesses in each industry sector, as defined by a 6-digit NAICS code. For example, entities defined as Pesticide and Other Agricultural Chemical Manufacturing (325320) are small if they employ 500 or fewer people; Pharmaceutical Preparation Manufacturing (325412) entities are small if they employ 750 or

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<sup>4</sup> Specifically, the SBA treats a firm that has a substantial portion of its assets and/or liabilities shared with a predecessor entity as part of that predecessor entity.

fewer people. Other entities are defined by sales. For example, Testing Laboratories (541380) are small entities if they have annual sales of \$5.0 million or less.

### 6.2.1 Estimation of the Number of Small Businesses

EPA used the following databases to estimate the number of businesses registering pesticides:

- Pesticide Regulatory Action Tracking System (PRATS) is used by EPA to track and manage registration activities.
- PPIS contains information on all pesticide products registered in the United States which includes all registered pesticide products and their registrants.
- D&B (Dunn & Bradstreet) is a comprehensive source of financial information on entities, including firm locations, sales, and primary business classifications under North American Industrial Classification System code (NAICS).includes financial and firm size data on many firms.

The PRATS sample includes 120 firms that would have incurred incremental costs as a result of the proposed rule had it been in place from 1996-2004. Of these, 97 ultimate parent entities were identified. Twenty-three firms had insufficient D&B financial data to be classified by SBA size definitions. (One small and one large firm had employee data but not revenue data in D&B.) Table 6.1 shows the size distribution of the 97 parent entities in the PRATS sample. Of these 97 parent companies, 51% are small and 49% are large.

**Table 6-1: Companies in the PRATS Sample by SBA Size**

Size <sup>2</sup>	Number of Parent Companies	Percentage of Parent Companies
Small	49	50.52%
Large	48	49.48%
<b>Total</b>	<b>97</b>	<b>100.00%</b>

Source: PRATS 2003, Dun & Bradstreet 2004.

<sup>1</sup> Twenty-three companies did not have sufficient Dun & Bradstreet (D&B) financial data to be classified by SBA size definitions.

<sup>2</sup> Size definitions vary according to the SBA small business definition associated with each NAICS code.

The PPIS database was queried in fall 2004 for all companies having one or more Section 3 or Section 24(c) (state) pesticide registrations. Companies with unique EPA company numbers in the PPIS database were consolidated based on the following criteria: (1) matching EPA company numbers with Dun & Bradstreet DUNS and ultimate parent DUNS numbers; (2) results of recent mergers and acquisitions; (3) matching company names associated with unique EPA company numbers; and (4) recommendations by EPA to be consolidated based on nearly

identical name matching and/or prior knowledge. As a result, 1,804 unique companies represent the total universe of conventional pesticide registrants.

An attempt was made to match all 1,804 unique pesticide registrants with company information (total revenue and number of employees) from the Dun & Bradstreet (D&B) database. We assume D&B company information is available for all relatively large companies. However, D&B company information is not easily collected or readily available for relatively small companies.

A D&B data analysis of the 1,804 pesticide registrants identified 146 SBA-defined large pesticide registrants. This was done in two ways. First, 116 companies were successfully identified as large through cross-referencing D&B company numbers and associated company information with EPA company numbers from the 1,804 companies identified in the PPIS database. Second, the remaining companies were manually reviewed and we determined 30 additional companies met the SBA definition as large. The average revenue and employee numbers were determined for the 146 large pesticide registrants based on the company information reported in the D&B database.

The remaining 1,658 pesticide registrants were considered small companies (1,804 - 146). The average revenue and employee number for small pesticide registrants was determined from a random sample because sufficient D&B company information was not available for many small registrants. A random sample of 1,000 companies was taken from the original PPIS registrant data set and matched with company information (total revenue and number of employees) queried from the D&B database. Sufficient D&B company information was available for 565 of the 1,000 sample companies for classifying companies as small or large according to SBA standards. Of the 565 sample companies classified, 449 met the SBA definition for small. The average revenue and employee number for these 449 companies is assumed to be representative for all small pesticide registrants.

## **6.2.2 Sales and Employees**

Tables 6.2 and 6.3 show the average sales and average number of employees for the parent entities in the PRATS and PPIS data set. The average sales for small parent entities in the PRATS data set is \$24.3 million and the average sales for large parent entities is \$9 billion. The average number of employees for small parent entities is 87, and the average number of employees for large parent entities is 33,274. The average sales for small parent entities in the PPIS data set is \$8.8 million, and the average sales for large parent entities is \$5 billion. In PPIS data, the average number of employees for small parent entities is 39, and the average number of employees for large parent entities is 18,681.

**Table 6-2: Average Sales and Employees – PRATS Data Set**

Size	Sales		Employees	
	Number of Parent Companies with Data <sup>1</sup>	Average Sales	Number of Parent Companies with Data	Average Number of Employees
Small	48	\$24,293,120	49	87
Large	47	\$9,074,010,059	48	33,274

Source: PRATS 2004, Dun & Bradstreet 2004.

<sup>1</sup> One small and one large company reported employee data but no revenue data to D&B.

**Table 6-3: Average Sales and Employees – PPIS Data Set**

Size	Number of Parent Companies	Average Sales	Average Number of Employees
Small	1658	\$8,840,000	39
Large	146	\$5,041,690,000	18,681

Source: PPIS, Dun & Bradstreet 2004

### 6.3 Small Business Impact Analysis

Potential impact is equal to cost as a percent of annual sales. Average cost to third party per study complying with the Common Rule is \$5,200. Average sales revenue for a small entity is equal to \$24 million. Potential impact to a small entity complying with the Common Rule is 0.02 percent (\$5,200 / \$24 million).

## 7 Limitation of the Economic Analysis

Estimating incremental costs of the four options was subject to uncertainty and also complicated due to the following factors.

### IRB review cost

This analysis is likely to overstate the IRB review costs per study because it is assumed that each human study is required to have a full IRB review. However, some human studies could qualify for an expedited review, which is not as costly as a full review. In this analysis we assumed all human studies submitted to EPA will require full review. IRB fees also vary depending on types and sizes of IRB institutions.

### Number of human studies submitted to EPA

Third-party human studies are most frequently related to pesticides. The number of studies used in this analysis was based on historical data, but the future submission may vary.

**Agency cost of reviewing the ethical aspects of protocols and completed human studies**

The Agency currently does not have established regulations for reviewing the ethical aspects of protocols and completed human studies by third parties. The burden and cost estimates for the Agency in this analysis are uncertain because they were derived from the Agency assumptions on burden hours and wages. In spite of these limitations, the incremental costs of the proposed rule to industry and the Agency are not likely more than \$1 million.

## Reference

- 1) C2C Ltd., (2005). “C2C IRB Fee Schedule.” <http://c2cirb.com>.
- 2) Independent Review Consulting (IRC), Inc (2005). “IRC-IRB 2005 Fee Schedule.” <http://www.irb-irc.net>.
- 3) New England Institutional Review Board (NEIRB) (2005). “NEIRB-IRB Fee Schedule.” <http://www.neirb.com>.
- 4) The Belmont Report (2005). “Ethical Principles and Guidelines for the Protection of Human Subjects of Research.” <http://www.hhs.gov/ohrp/humansubjects/guidance/belmon.htm>.
- 5) The Declaration of Helsinki (2005). <http://www.wma.net/e/policy/b3.htm>.
- 6) The Scranton-Temple Residency Program (STRP) (2005). “STRP-IRB Fee Schedule.” <http://www.strpweb.org>.
- 7) The Oregon Health Science University Cancer Institute (OHSU) (2005). “OHSU-IRB Fee Schedule.” <http://www.ohsucancer.com>.
- 8) The Federal Food and Drug Administration (FDA) (year?). “Supporting Statement Protection of Human Subjects Recordkeeping Requirements for Institutional Review Boards.” Docket No. 2004N-0114.
- 9) The U.S. National Institute of Health. <http://clinicaltrials.gov>
- 10) US EPA (2005). “Human Study Submission to the Office of Pesticides Programs by Year” Office of Pesticides Programs.
- 11) US EPA(2005). “Methodology to Estimate the Personal Wages Associated with the Reporting of Information Collection Request.” Draft. Office of Pesticide Program.
- 12) US EPA (2000). “Guidelines for Preparing Economic Analyses.” Office of the Administrator.

## Appendix A: Calculation of IRBC per Human Study

**Table A-1: Calculation of IRBC per Human Study**

	NEIRB (1)	C2C (2)	IRC (3)	STRP (4)	OHSU (5)
Initial Review (A)	\$1,350	\$1,250	\$1,350	\$2,000	\$1,400
Annual Continuing Review (4 times) (B)	\$2,400	\$2,800	\$3,200	\$2,000	\$3,360
Revision and Amendments (1 time) (C)	\$400	\$200	\$500	\$500	\$525
IRB Fee (A + B + C)	\$4,150	\$4,250	\$5,050	\$4,500	\$5,285
Cost to Principle Investigator (10% of Average IRB Fee)	\$415	\$425	\$505	\$450	\$529
IRBC in the Analysis	\$4,565	\$4,675	\$5,555	\$4,950	\$5,814

Source:

1) New England Institutional Review Board (NEIRB) (2005). “NEIRB-IRB Fee Schedule.” <http://www.neirb.com>.

2) C2C Ltd., (2005). “C2C IRB Fee Schedule.” <http://c2cirb.com>.

3) Independent Review Consulting (IRC), Inc (2005). “IRC-IRB 2005 Fee Schedule.” <http://www.irb-irc.net>.

4) The Scranton-Temple Residency Program (STRP) (2005). “STRP-IRB Fee Schedule.” <http://www.strpweb.org>.

5) The Oregon Health Science University Cancer Institute (OHSU) (2005). “OHSU-IRB Fee Schedule.” <http://www.ohsucancer.com>.

**Appendix B: Human Study Submissions to the Office of Pesticide Program, 1996-2001**

**Table B-1: Human Study Submissions to the Office of Pesticide Program, 1996-2001**

	1996	1997	1998	1999	2000	2001	Average
Studies not involving intentional Exposure	21	32	30	33	26	30	32
Studies involving intentional exposure (A+B+C+D+E)	29	45	22	33	19	30	30
A) Pesticide handler or re-entry Exposure	3	3	3	7	4	4	4
B) Skin test for irritancy, sensitization, or photoresponse	15	20	4	8	3	10	10
C) Systemic toxicity	0	6	4	6	5	4	4
D) Absorption or Pharmacokinetics (or Metabolism in humans)	4	3	4	4	4	1	3
E) Insect Repellent Efficacy	7	13	7	8	3	11	8
Total human studies submitted to OPP	52	80	54	73	48	63	62

Source: US EPA (2005). "Human Study Submission to the Office of Pesticides Programs by Year." Office of Pesticide Programs

**Appendix C: Industry and Agency Cost Estimation for Each Option**

**Table C-1: Industry and Agency Cost Estimation for Option 1 (Low Cost)**

Option 1 with low IRBC cost							
	Option 1	Baseline	Incremental Cost				
<b>Cost to Industry</b>	<b>\$158,760</b>	<b>\$158,760</b>	<b>\$0</b>				
<b>Cost to the Agency</b>	<b>\$112,530</b>	<b>\$112,530</b>	<b>\$0</b>				
<b>Cost to third parties</b>							
	IRBC	IRC	IPC	Unit Cost per study	# of studies	Cost to third parties	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$4,565	\$727	\$0	\$5,292	10	\$52,920	
System toxicity	\$4,565	\$727	\$0	\$5,292	4	\$21,168	
Other intentional exposure studies	\$4,565	\$727	\$0	\$5,292	16	\$84,672	
					Total	\$158,760	
<b>Cost to the Agency</b>							
	ARC	APC		Unit Cost per study	# of studies	Cost to the Agency	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$3,751	\$0		\$3,751	10	\$37,510	
System toxicity	\$3,751	\$0		\$3,751	4	\$15,004	
Other intentional exposure studies	\$3,751	\$0		\$3,751	16	\$60,016	
					HSRBC	\$0	
					Total	\$112,530	

**Table C-2: Industry and Agency Cost Estimation for Option 1 (High Cost)**

Option 1 with high IRBC cost							
	Option 1	Baseline	Incremental Cost				
<b>Cost to Industry</b>	<b>\$196,350</b>	<b>\$196,350</b>	<b>\$0</b>				
<b>Cost to the Agency</b>	<b>\$112,530</b>	<b>\$112,530</b>	<b>\$0</b>				
<b>Cost to third parties</b>							
	IRBC	IRC	IPC	Unit Cost per study	# of studies	Cost to third parties	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$5,818	\$727	\$0	\$6,545	10	\$65,450	
System toxicity	\$5,818	\$727	\$0	\$6,545	4	\$26,180	
Other intentional exposure studies	\$5,818	\$727	\$0	\$6,545	16	\$104,720	
					Total	\$196,350	
<b>Cost to the Agency</b>							
	ARC	APC		Unit Cost per study	# of studies	Cost to the Agency	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$3,751	\$0		\$3,751	10	\$37,510	
System toxicity	\$3,751	\$0		\$3,751	4	\$15,004	
Other intentional exposure studies	\$3,751	\$0		\$3,751	16	\$60,016	
					HSRBC	\$0	
					Total	\$112,530	

**Table C-3: Industry and Agency Cost Estimation for Option 2 (Low Cost)**

Option 2 with low IRBC cost							
	Option 2	Baseline	Incremental Cost				
<b>Cost to Industry</b>	<b>\$166,292</b>	<b>\$158,760</b>					
<b>Cost to the Agency</b>	<b>\$333,424</b>	<b>\$112,530</b>					
<b>Cost to third parties</b>							
	IRBC	IRC	IPC	Unit Cost per study	# of studies	Cost to third parties	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$4,565	\$727	\$538	\$5,830	10	\$58,300	
System toxicity	\$4,565	\$727	\$538	\$5,830	4	\$23,320	
Other intentional exposure studies	\$4,565	\$727	\$0	\$5,292	16	\$84,672	
					Total	\$166,292	
<b>Cost to the Agency</b>							
	ARC	APC		Unit Cost per study	# of studies	Cost to the Agency	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$2,091	\$4,581		\$6,672	10	\$66,720	
System toxicity	\$2,091	\$4,581		\$6,672	4	\$26,688	
Other intentional exposure studies	\$3,751	\$0		\$3,751	16	\$60,016	
					HSRBC	\$180,000	
					Total	\$333,424	

**Table C-4: Industry and Agency Cost Estimation for Option 2 (High Cost)**

Option 2 with high IRBC cost			
	Option 2	Baseline	Incremental Cost
<b>Cost to Industry</b>	<b>\$203,882</b>	<b>\$196,350</b>	<b>\$7,532</b>
<b>Cost to the Agency</b>	<b>\$333,424</b>	<b>\$112,530</b>	<b>\$220,894</b>

	IRBC			Unit Cost per study	# of studies	Cost to third parties
	IRBC	IRC	IPC			
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$5,818	\$727	\$538	\$7,083	10	\$70,830
System toxicity	\$5,818	\$727	\$538	\$7,083	4	\$28,332
Other intentional exposure studies	\$5,818	\$727	\$0	\$6,545	16	\$104,720
					Total	\$203,882

	ARC		Unit Cost per study	# of studies	Cost to the Agency
	ARC	APC			
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$2,091	\$4,581	\$6,672	10	\$66,720
System toxicity	\$2,091	\$4,581	\$6,672	4	\$26,688
Other intentional exposure studies	\$3,751	\$0	\$3,751	16	\$60,016
				HSRBC	\$180,000
				Total	\$333,424

**Table C-5: Industry and Agency Cost Estimation for Option 3 (Low Cost)**

Option 3 with low IRBC cost						
	Option 3	Baseline	Incremental Cost			
<b>Cost to Industry</b>	<b>\$174,900</b>	<b>\$158,760</b>	<b>\$16,140</b>			
<b>Cost to the Agency</b>	<b>\$440,160</b>	<b>\$112,530</b>	<b>\$327,630</b>			
<b>Cost to third parties</b>						
	IRBC	IRC	IPC	Unit Cost per study	# of studies	Cost to third parties
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$4,565	\$727	\$538	\$5,830	10	\$58,300
System toxicity	\$4,565	\$727	\$538	\$5,830	4	\$23,320
Other intentional exposure studies	\$4,565	\$727	\$538	\$5,830	16	\$93,280
					Total	\$174,900
<b>Cost to the Agency</b>						
	ARC	APC		Unit Cost per study	# of studies	Cost to the Agency
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$2,091	\$4,581		\$6,672	10	\$66,720
System toxicity	\$2,091	\$4,581		\$6,672	4	\$26,688
Other intentional exposure studies	\$2,091	\$4,581		\$6,672	16	\$106,752
					HSRBC	\$240,000
					Total	\$440,160

**Table C-6: Industry and Agency Cost Estimation for Option 3 (High Cost)**

Option 3 with high IRBC cost							
	Option 3	Baseline	Incremental Cost				
<b>Cost to Industry</b>	<b>\$212,490</b>	<b>\$196,350</b>					
<b>Cost to the Agency</b>	<b>\$440,160</b>	<b>\$112,530</b>					
<b>Cost to third parties</b>							
	IRBC	IRC	IPC	Unit Cost per study	# of studies	Cost to third parties	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$5,818	\$727	\$538	\$7,083	10	\$70,830	
System toxicity	\$5,818	\$727	\$538	\$7,083	4	\$28,332	
Other intentional exposure studies	\$5,818	\$727	\$538	\$7,083	16	\$113,328	
					Total	\$212,490	
<b>Cost to the Agency</b>							
	ARC	APC		Unit Cost per study	# of studies	Cost to the Agency	
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$2,091	\$4,581		\$6,672	10	\$66,720	
System toxicity	\$2,091	\$4,581		\$6,672	4	\$26,688	
Other intentional exposure studies	\$2,091	\$4,581		\$6,672	16	\$106,752	
					HSRBC	\$240,000	
					Total	\$440,160	

**Table C-7: Industry and Agency Cost Estimation for Option 4 (Low Cost)**

Option 4 with low IRBC cost						
	Option 3	Baseline	Incremental Cost			
<b>Cost to Industry</b>	<b>\$361,460</b>	<b>\$158,760</b>	<b>\$202,700</b>			
<b>Cost to the Agency</b>	<b>\$713,664</b>	<b>\$112,530</b>	<b>\$601,134</b>			
<b>Cost to third parties</b>						
	IRBC	IRC	IPC	Unit Cost per study	# of studies	Cost to third parties
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$4,565	\$727	\$538	\$5,830	10	\$58,300
System toxicity	\$4,565	\$727	\$538	\$5,830	4	\$23,320
Other intentional exposure studies	\$4,565	\$727	\$538	\$5,830	16	\$93,280
Human studies not involving human exposure	\$4,565	\$727	\$538	\$5,830	32	\$186,560
					Total	\$361,460
<b>Cost to the Agency</b>						
	ARC	APC		Unit Cost per study	# of studies	Cost to the Agency
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$2,091	\$4,581		\$6,672	10	\$66,720
System toxicity	\$2,091	\$4,581		\$6,672	4	\$26,688
Other intentional exposure studies	\$2,091	\$4,581		\$6,672	16	\$106,752
Human studies not involving human exposure	\$2,091	\$4,581		\$6,672	32	\$213,504
					HSRBC	\$300,000
					Total	\$713,664

**Table C-8: Industry and Agency Cost Estimation for Option 4 (High Cost)**

Option 4 with high IRBC cost						
	Option 3	Baseline	Incremental Cost			
<b>Cost to Industry</b>	<b>\$439,146</b>	<b>\$196,350</b>	<b>\$242,796</b>			
<b>Cost to the Agency</b>	<b>\$713,664</b>	<b>\$112,530</b>	<b>\$601,134</b>			
<b>Cost to third parties</b>						
	IRBC	IRC	IPC	Unit Cost per study	# of studies	Cost to third parties
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$5,818	\$727	\$538	\$7,083	10	\$70,830
System toxicity	\$5,818	\$727	\$538	\$7,083	4	\$28,332
Other intentional exposure studies	\$5,818	\$727	\$538	\$7,083	16	\$113,328
Other studies not involving human exposure	\$5,818	\$727	\$538	\$7,083	32	\$226,656
					Total	\$439,146
<b>Cost to the Agency</b>						
	ARC	APC		Unit Cost per study	# of studies	Cost to the Agency
Skin Tests for Irritancy, Sensitization, or Photoresponse	\$2,091	\$4,581		\$6,672	10	\$66,720
System toxicity	\$2,091	\$4,581		\$6,672	4	\$26,688
Other intentional exposure studies	\$2,091	\$4,581		\$6,672	16	\$106,752
Other studies not involving human exposure	\$2,091	\$4,581		\$6,672	32	\$213,504
					HSRBC	\$300,000
					Total	\$713,664

## **Appendix D: Industry Profile**

This profile relies on a number of sources of information on the pesticide industry. The major sources include the following:

- EPA Office of Pesticide Programs (OPP) publications and estimates
- Pesticide industry profiles prepared for previous regulatory analyses for EPA's Offices of Pesticide Programs, Water, and Air
- Industry profiles prepared by private research firms
- Dunn & Bradstreet industry data
- Research on specific companies using publicly available business databases accessed through the Internet
- Searches of academic and industry literature
- Economic Census data from the U.S. Census Bureau
- Other U.S. Department of Commerce sources

### **Use of Census Data**

Whenever a data source contained complete information to illustrate a certain aspect of the pesticide industry, we chose to present that information. In other cases, the only source of national level information was the U.S. Census Bureau's Economic Census of Manufacturers. There are inherent difficulties associated with using data from the Economic Census performed by the U.S. Census Bureau to characterize certain industrial sectors contained in this profile.

The Census Bureau has recently revised its industry classification system and now uses "North American Industrial Classification System" (NAICS) codes to describe industrial sectors. Information in the 1997 Census is organized according to the NAICS. The NAICS replaces the Standard Industrial Classification (SIC) system that had been used in all earlier Census publications. NAICS assignment for an establishment is made according to one of 20 major industrial sectors. These sectors are further divided into 96 subsectors, 313 industry groups, and 1,170 industries.

In some cases, the relevant Census data required for this economic profile was available at a sufficiently disaggregated level that it corresponds reasonably accurately to the establishments in the industrial sectors of interest here. In other cases, the Census categorization reflects a very large and diverse industry, of which the relevant sector may be a small part. Finally, many pesticide industry participants are classified into entirely different Census industry categories because their primary product is not related to pesticides. In the latter cases, the Census data do not provide a precise representation of the characteristics of establishments of interest.

Exhibit D.1 provides descriptions of the NAICS categories used to present Census data for each sector examined in this profile. It also indicates whether NAICS-based data correspond to SIC-based data over time. The Census categories used for each of the major pesticide industry sectors included in this profile and their relative precision as a measure of the pesticide and related industries are discussed in more detail below.

Exhibit D.1: Census Industry Classifications Used in Profile			
Profile Sector	NAICS/ SIC	Description	SIC - NAICS Correspondence
Conventional Active Ingredient Producers and Formulators, Packagers, and Repackagers	325199/ 2869	All Other Basic Organic Chemical Manufacturing	no
	325320/ 2879	Pesticide and Other Agricultural Chemical Manufacturing	yes
Source: U.S. Department of Commerce, 1992 and 1997.			

EPA has incorporated data from several public sources in addition to using the Economic Census. For the most part, these sources continue to use the SIC system to organize and present information. These data are noted as SIC-based data in the text. EPA uses time series data from these sources because of the consistent categorization of industry groups across time.

### General Pesticide Industry Description

Pesticides are important products that play a significant role in many aspects of the economy. They are used by diverse economic sectors such as agriculture, industry, and residential. Pesticides reduce or eliminate undesirable weeds, insects, animals, fungi, and bacteria and are used to preserve wood and regulate plant growth. All of these pesticide uses produce desirable outcomes such as increased agricultural productivity and improved human health. However, due to their nature, their use also implies some environmental and health risks (U.S. EPA, 1999c).

Pesticide products themselves fall into several categories: conventional pesticides, specialty and niche pesticides, and antimicrobial pesticides. Conventional pesticides are those products that are commonly available to users including herbicides (weed killers), insecticides (“bug” killers), and fungicides (fungus killers), as well as some special classifications such as fumigants used to sterilize soil to remove pathogens. The vast majority of pesticides used in the U.S. fall into this category.

Pesticide production involves combining a more than one substance into a formulation. The main ingredient of a pesticide product is the active ingredient: the chemical that is toxic to the targeted pest. Some pesticide formulations contain more than one active ingredient, depending on their target or targets. These pesticide active ingredients, or active ingredients, cannot be applied in their basic form for reasons of safety and effectiveness. EPA regulates both active ingredients and formulations through a registration process. There are roughly 890 active ingredients registered with EPA, and nearly 18,000 registered formulations. Depending on the context or the data source, this profile will make a distinction between discussions of active ingredient and discussions of formulations. Exhibit D.2 presents a summary of the number of regulated conventional pesticide products and tolerances.

Exhibit D.2: Regulated Pesticide Products	
Product Segment	Number of Products
Active Ingredients with Active Registrations (Federal and State)	891
Active Ingredients with Food/Feed Tolerances (September 1998)	523
Formulated Products with Federal Registrations (June 1998)	17,713
Tolerances in Place (September 1998)	9,783
Source: U.S. EPA, 1999c	